

Integrated clinical management and neurorehabilitation for lumbosacral spinal diseases

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Integrated clinical management and neurorehabilitation for lumbosacral spinal diseases

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Editorial: Integrated clinical management and neurorehabilitation for lumbosacral spinal diseases

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lumbosacral spinal disease, treatment, neurorehabilitation, sphincter function, integrated medicine

Editorial on the Research Topic

Integrated clinical management and neurorehabilitation for lumbosacral spinal diseases

The management of lumbosacral spinal diseases—spanning degenerative, oncologic, congenital, and traumatic pathologies—remains a complex challenge that demands a balance between innovation and validation. Recent studies highlight promising tools and therapies, but they also expose critical gaps in evidence, reproducibility, and clinical translation (1–5). This editorial summarizes key findings from the current Research Topic while emphasizing methodological limitations, unresolved questions, and actionable recommendations to steer future research toward meaningful patient-centered outcomes.

The integration of advanced imaging and computational modeling has undeniably improved diagnostic precision. One example from our own research is the development of an arbitrary-dimensional nerve root reconstruction MRI (ANRR-MRI) technique that offers a novel method to identify leakage points in sacral meningeal cysts, thereby enabling more targeted surgical interventions. While the reported 100 postoperative cyst resolution in 40 patients is notable, the lack of long-term follow-up data may raise concerns about recurrence rates and the durability of the results (Yang et al.) (6). Additionally, the homogeneity of the cohort (all patients were treated at a single center) limited the generalizability of the findings. Validation in diverse populations, including those with multifocal cysts or concurrent spinal abnormalities, is essential before ANRR-MRI can be widely adopted as a standard diagnostic tool. Similarly, Chen et al.'s machine learning model for predicting 1-year postoperative recovery in patients with lumbar disk herniation demonstrated the potential of artificial intelligence in personalized care (Chen et al.) (7). However, reliance on retrospective data from a single institution introduced inherent biases, and the model's performance metrics—while superior to other algorithms—lacked transparency in feature importance. Clinicians cannot trust a “black box” without understanding which variables (e.g., preoperative pain scores, comorbidities, or socioeconomic factors) drive predictions (8, 9). Future studies must prioritize interpretability and external validation across healthcare systems to avoid perpetuating biased algorithms.

Therapeutic advances, while innovative, frequently overlook cost-effectiveness and scalability. The study by Tan et al. on uniportal full-endoscopic (UFE) surgery for lumbar facet joint cysts under local anesthesia reported impressive pain relief and functional improvement in eight patients (Tan et al.) (10). However, the exclusion of patients with comorbidities or multilevel pathology, which is common in real-world practice, called into question the study's generalizability. Additionally, the small sample size and the absence of a control group (e.g., comparing UFE to conventional open surgery) also precluded definitive conclusions about UFE's superiority. Similarly, deep brain stimulation (DBS) for spinal cord injury (SCI) recovery has been praised for its neuromodulatory potential; however, the reviewed preclinical and clinical evidence remained fragmented. The majority of studies focus on acute injury models, ignoring chronic SCI cases in which neuroplasticity is diminished. Moreover, the emphasis on motor recovery overlooks potential autonomic benefits (e.g., bladder control), which are equally critical to patient quality of life. Without standardized protocols for DBS target selection, stimulation parameters, and rehabilitation integration, the therapy risks becoming a costly, unproven intervention rather than a scalable solution.

Although rehabilitation strategies are foundational to care, they often lack mechanistic rigor. The meta-analysis by Liu et al. advocated for suspension exercise training (SET) in lumbar disk herniation, citing significant improvements in pain and functional scores (Liu et al.) (11). However, high heterogeneity in outcomes ($I^2 = 86\text{--}92\%$) undermined confidence in its efficacy. Subgroup analyses suggested that SET combined with traditional Chinese medicine (TCM) yields better results than SET alone; however, the inclusion of TCM—a variable with its own unverified mechanisms—complicated the attribution of benefits. Are the improvements due to SET, TCM, or placebo effects? The study design did not disentangle these factors. Similarly, the GIGER MD biofeedback device for neurogenic bladder in children was shown to increase voiding capacity and reduce incontinence, but the 36-patient cohort lacked a control group, and the 6-month follow-up period was insufficient to assess sustained benefits. Rehabilitation research must adopt more rigorous methodologies, including sham-controlled trials and mechanistic studies, to isolate therapeutic effects from confounding variables.

The oncologic studies in this collection revealed the ongoing challenges of managing aggressive pathologies. The sacral chordoma cohort analysis identified lung metastasis as a key prognostic factor, with larger tumors and postoperative recurrence correlating with poorer survival (Shi et al.) (12). While these findings aligned with existing literature, the retrospective design and reliance on radiographic diagnoses (without biopsy confirmation in all cases) introduced potential misclassification bias. Furthermore, the study did not address the role of emerging therapies, such as targeted molecular agents, in the treatment of metastatic chordoma (13). Similarly, a case report of adult lumbosacral neuroblastoma highlighted the rarity of this malignancy but offered limited insight into optimal management. The decision to prioritize chemotherapy over radical resection reflects institutional bias rather than evidence-based

consensus, emphasizing the need for collaborative registries to pool data and establish standardized guidelines for rare spinal tumors.

Given these limitations, we developed several recommendations. First, methodological transparency must be prioritized. Studies leveraging machine learning should publish their code and datasets to enable replication. Second, clinical trials—whether surgical or rehabilitative—must incorporate control arms and longer follow-up periods to distinguish treatment effects from the natural progression of the condition. Third, cost-effectiveness analyses are non-negotiable. Innovations such as UFE surgery and DBS will fail to translate into widespread practice if their benefits do not outweigh the economic burden on healthcare systems. Fourth, collaborative efforts to harmonize measures such as the ODI or JOA across institutions would reduce heterogeneity and enable meta-analyses with greater statistical power. Fifth, research should explicitly evaluate access barriers to advanced diagnostics (e.g., ANRR-MRI) or therapies (e.g., gene-targeted SMA drugs) in low-resource regions, rather than assuming scalability.

Finally, the field must move beyond symptom-centric outcomes. While pain and functional scores are important, patient-reported outcomes—such as mental health, social participation, and caregiving burden—are rarely measured. For example, while SMA therapies such as nusinersen improve motor function, their impact on familial stress and financial toxicity remains unstudied. Similarly, DBS studies for SCI focus on gait recovery but neglect bladder and bowel function, which patients often rank as higher priorities. A paradigm shift toward holistic, patient-defined endpoints is overdue.

In conclusion, the studies in this Research Topic illustrate both the promise and pitfalls of contemporary lumbosacral spinal care. While technological and therapeutic advances abound, their clinical value remains uncertain without critical appraisal, methodological rigor, and a commitment to equity. Researchers must resist the allure of novelty and instead embrace stability and patient partnership to ensure that progress translates into meaningful, accessible outcomes. The path forward requires not just smarter tools, but also wiser stewardship of innovation.

Author contributions

MR: Project administration, Writing – original draft, Writing – review & editing. CY: Conceptualization, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

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Rehabilitation approach and results of using the biofeedback method (GIGER MD device) in children with neurogenic bladder

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Background: GIGER MD device applies a biofeedback method through stimulated coordinated rhythmic and dynamic movements of the trunk and extremities in an anti-gravity position, thus helping to regain lost motor functions.

Methods: In this article, the performance of the GIGER MD device was evaluated in 36 children with neurogenic bladder measuring gait speed, voiding bladder capacity, deviation from the age-adjusted bladder capacity (measured using the Koff scale), and urinary incontinence.

Results: Children using the GIGER MD device had an increase in voiding bladder capacity (33.79%, median volume increase of 50ml) with a subsequent median decrease in median age-adjusted bladder capacity by 45.50% (median deviation before was 36% vs. 16% after treatment). The number of urinary incontinence episodes also reduced by 55.57% (7–3 episodes *per day*), and the 20-meter motor gait speed increased by 14.26% (from 23 to 19s).

Conclusion: Children who follow the GIGER MD therapy regularly for a period of 6months show that CNS functional damage can be significantly improved.

KEYWORDS

GIGER MD, rehabilitation, neurogenic bladder, children, spina bifida

Introduction

Rehabilitation of children requires a multidisciplinary approach that uses brain neuroplasticity to stimulate and develop normal motor patterns of posture and movement (1–3). GIGER MD device uses biofeedback through stimulated coordinated rhythmic and dynamic movements of limbs and trunks in an anti-gravity position (4). Rhythmically and repetitively aligned movements encourage relearning of the central nervous system (CNS) functions and stimulate receptors on the skin, muscles, and joints. Repetition of such movements forms a new set of impulses which leads to the reorganization of the nervous system. Such stimulated

movements help restore the motor, vegetative, and higher mental functions lost to CNS damage. Children achieve new automaticity in movements and body posture. Children exposed to neuro-risk factors who have developed clinically significant symptoms of deviation from proper psychomotor development can be directed toward normal development through a habilitation program. There is a broad spectrum of indications for GIGER MD therapy, with mainly neurological and musculoskeletal damage and diseases mentioned. To date, no contraindications have been described (5). Reports of this method are an exception in the literature. This paper, therefore, aims for a dual purpose: (1) to provide information about the existence of this method and its possibilities and (2) to present the results we achieved by applying this method in children with neurogenic bladder.

Materials and methods

This retrospective case series included 36 children with neurogenic bladder as a common feature. Alongside neurogenic bladder, the patients also had congenital anomalies, and spinal cord and/or CNS damage. Twenty-five out of 36 children were also diagnosed with paraplegia prior to enrollment in the study. Because of the sensitivity of the GIGER MD procedure on children with neurological damage, we did not find an indication for applying this method in healthy children. For all children included in the research, measurements of 20-meter gait speed, the number of rotations performed per week, bladder capacity, and urine incontinence episodes were taken prior to enrollment and after a treatment period of 6 months. In 36 children with a diagnosis of neurogenic bladder, the parents kept a 48-h diary, both before and after the therapy, which was handed to them. Self-urinating children urinated into volume containers to obtain voided urine volume (mL), while catheterized children's volumes were measured *via* catheter bags. Children with nocturia were woken by their parents 1 and 4 h after falling asleep and offered to urinate. Age-adjusted bladder capacity was estimated using Koff's equation: expected capacity (mL) = [age + 1] × 30 (6). Using the aforementioned equation, we calculated the deviation from the expected bladder capacity and expressed the deviation in percentages. The number of incontinent episodes per day was monitored over a week, and the average was taken. There is no published literature data on the use of biofeedback (GIGER MD) device in patients with neurogenic bladder.

Statistical analysis

The following variables were measured before and after GIGER MD therapy (gait speed, voiding bladder capacity, deviation from the Koff scale, urinary incontinence). Data are expressed as mean, standard deviation, median, and interquartile range (IQR). The difference between paired variables was analyzed using a two-sample paired (Wilcoxon) signed rank test. The Spearman correlation coefficient was applied to assess the strength of a monotonic relationship between paired variables (6). A correlation matrix heatmap was used to clearly show the relationships of individual groups of children for the same

parameters before and after therapy. A correlation heatmap showed the graphical representation of the correlation between different variables. All applied tests were two-tailed, and *p*-values ≤ 0.05 were acknowledged as statistically significant. Statistical analysis was performed with the program GraphPad Prism 8.4.3.686.

Results

A total of 36 children were enrolled in the study spanning three to 6 months. 25/36 children (A) had a gait assessment, while 36/36 (B) underwent voiding bladder capacity measurement estimation and urinary incontinence frequency. 11/36 children had no gait assessment. There was no difference in training between A and B groups.

The first group of children (A) had an age mean of 12.51 (+/− 4.1) years with a median of 12.33 years (9.792–14.50) and a male-to-female ratio of 1:2.1. The youngest child in the group was 7 years of age. The average group gait speed median before treatment measured 23 s (IQR 19.5–25), while after treatment, the median speed reduced to 19 s (IQR 15–22.5). The 20-meter gait speed after treatment increased by 14.26%, Wilcoxon signed rank test (two-tailed, *p* < 0.0001, Z-statistic 3.945). The results are shown in Figure 1.

The second group of children (B) had an age mean of 12.15 (+/− 4.51) years with a median of 11.34 years (IQR 8.790–14.19) and a male-to-female ratio of 1:2.17. The average group voiding bladder capacity median before treatment measured 200 (IQR 165–250) milliliters, while after treatment, the median volume increased to 250 (IQR 200–300) milliliters. The voiding bladder capacity after treatment increased by 33.79%, Wilcoxon signed rank test (two-tailed, *p* < 0.0001, Z-statistic −4.84). The results are shown in Figures 1A, 2.

The average median deviation from the Koff scale before treatment measured 36 (IQR 24–54.5) percent, while after treatment, the median deviation decreased to 16 (IQR 9–39) percent. After treatment, the deviation from the Koff formula decreased by 45.40%, Wilcoxon signed rank test (two-tailed, *p* < 0.0001, Z-statistic 4.55). The results are shown in Figure 2.

The average median urinary incontinence episodes measured 7 (IQR 4–9) *per* day, while after treatment, the number of episodes decreased to 3 (IQR 1–4) *per* day. Episodes of urinary incontinence were reduced by 55.57%, Wilcoxon signed-rank test (two-tailed, *p* < 0.0001, z-statistic 4.52). The results are shown in Figure 2.

Children with gait assessment had reduced voiding bladder capacity (mean 153 +/− 65.43 ml vs. 219.1 +/− 49.72 ml, value of *p* 0.043) and had a higher deviation from the Koff scale (mean 48.31 +/− 26.24% vs. 27.81 +/− 13.88, *p* = 0.092) vs. children with no gait assessment. There were no statistical differences between other parameters (Mann–Whitney *U*-test).

Spearman's rank correlation coefficient was used to assess the relationship between the variables. The variable of gait speed (*ρ* = −0.63) shows a strong negative correlation to the number of rotations per week. The voiding bladder capacity (*ρ* = 0.46) shows a moderate positive, while simultaneously, the decrease in deviation from the Koff scale shows a moderate negative (*ρ* = −0.51) correlation (Table 3).

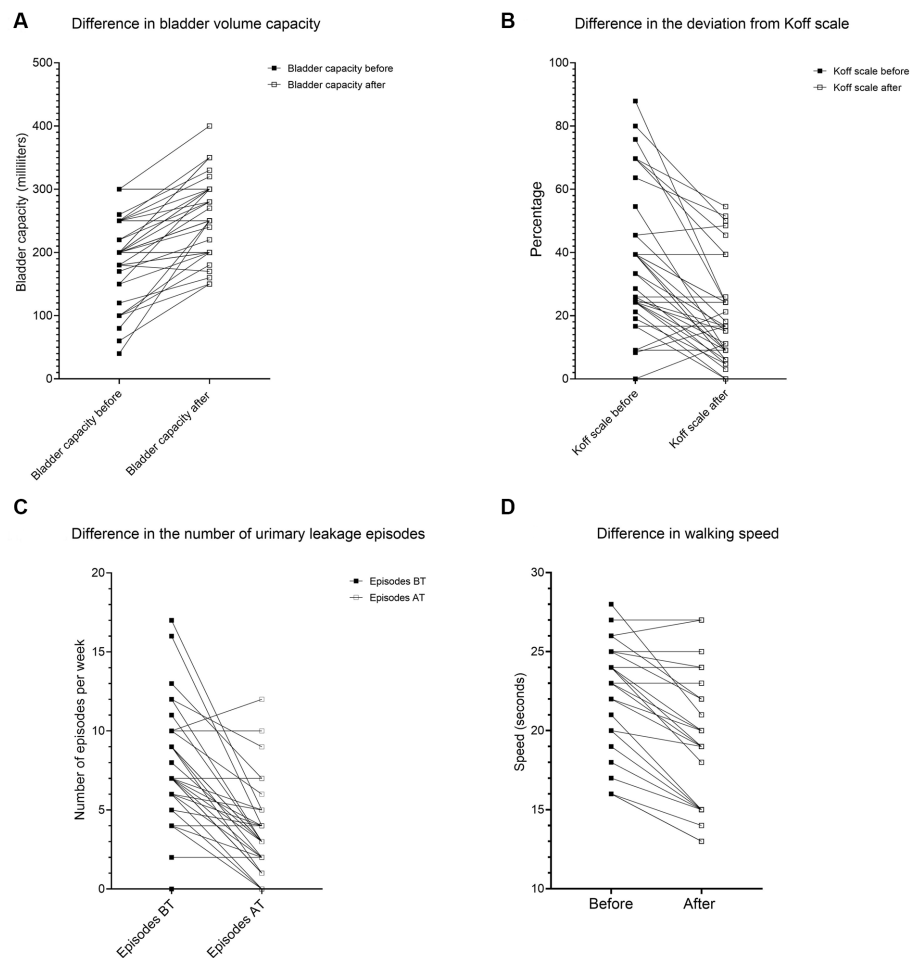


FIGURE 1

The difference in (A) bladder volume capacity, (B) deviation from the Koff scale, (C) gait speed, and (D) urinary leakage episodes.

Discussion

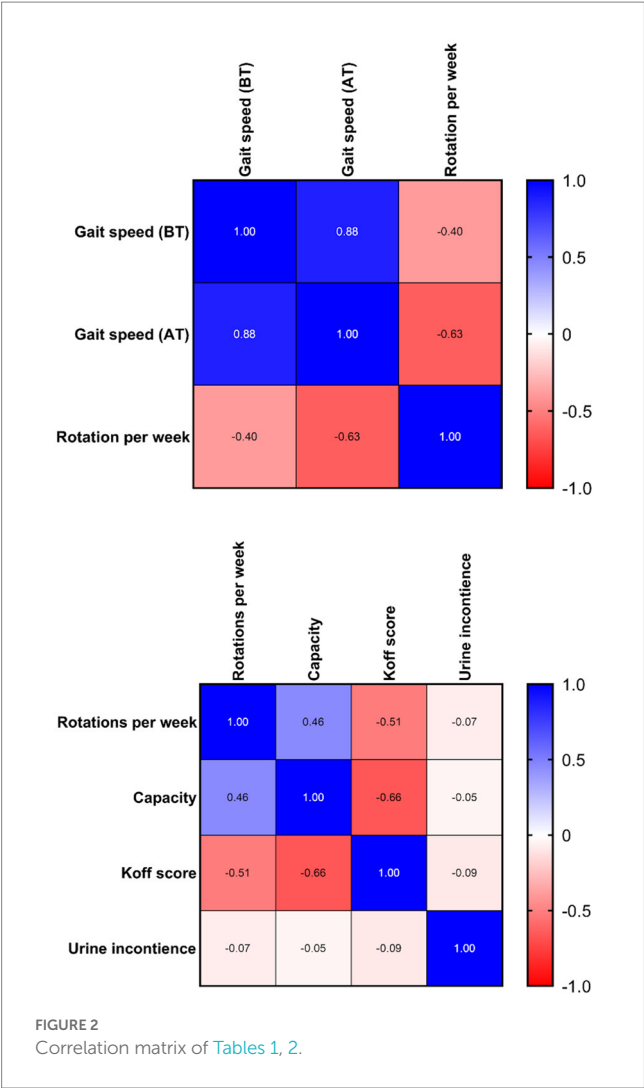
The primary *modus operandi* of the GIGER MD® device consists of coordinated movements of arms and legs *via* hand and foot pedals, which are triggered in different phases from each other. Children who could perform gait assessment had a greater overall benefit from biofeedback therapy vs. children without gait assessment.

Spine movements are performed in the frontal, sagittal, and horizontal planes. Such stimulated movements are as follows: rotation, movement to the left and right, and elongation and shortening. In the supination position, the child alternates the following positions: basic, extension, flexion, and traction positions. A damaged neural pathway can be reorganized if rhythmic, dynamic, and symmetrical movements of the limbs and trunk activate it. The injured part of the neurological system is activated simultaneously with the activation of the surrounding healthy parts of the neurological system, whereby the damaged part learns from the healthy how to restore the lost function. The key is to activate a significantly larger area of the healthy part simultaneously with the injured part. In that way, the healthy part avoids the dominance of the damaged part. It is important to

achieve reintegration and coordination of the arms, legs, hands, fingers, trunk, and head motor functions with auditory, visual, and higher mental functions (3).

Brain neuroplasticity is significantly more pronounced during growth and development in children (7). In order to restore the functions of the damaged areas of the CNS, enough appropriate impulses must arrive from the periphery to be processed and restore normal functioning. In paraplegic patients, rhythmically coordinated movements GIGER MD device stimulates the base of the brain stem, while at the same time, hand movements stimulate the cerebellum. Spiral (circular) movements of the body, in turn, activate the locomotor center in the spinal cord. Repeating such movements forms a new set of impulses that reorganizes the nervous system and achieves new automaticity in movements and body posture. This applies to patients with spinal cord injuries, cerebral palsy, Parkinson's disease, stroke, and idiopathic scoliosis. It is also used in several other neurological conditions, such as peripheral nervous system diseases and spina bifida.

A therapeutic approach to the neurogenic bladder is a challenging one. Despite numerous (re)habilitation procedures, this sub-area has



not been definitively resolved so far and belongs to the domain of future answers.

Contemporary treatment is now reduced to several recommendations (1) clean intermittent catheterization (2) reflex voiding and bladder expression with Valsalva or Credé (3) condom catheter drainage or indwelling catheters such as urethral catheters or suprapubic tube (4) urinary diversion by ileal conduit if self-catheterization is impossible (5) suppressing neurogenic detrusor overactivity or compliance alteration (anticholinergics, intra-detrusor botulinum toxin) (6) aponeurotic suburethral tape or artificial urinary sphincter for sphincter insufficiency (7) Transcutaneous Electrical Stimulation for Neurogenic Bladder Dysfunction (8) resorting to surgery is sometimes necessary either after the failure of non-invasive treatments (e.g., bladder augmentation in case of neurogenic detrusor overactivity. Resistant to pharmacological treatment) (8–12). We here present the GIGER MD method, which may be able to improve some neurogenic bladder treatment procedures. In all these circumstances GIGER MD treatment can still be performed in cases of all the above-mentioned diagnoses.

TABLE 1 Age, number of rotations and the difference in gait speed, bladder capacity, Koff scale and number of urinary incontinence before and after GIGER MD therapy.

Variable	Mean (SD)	Median (IQR)
Group age (N=38)	12.15 (4.5)	11.34 (8.8 to 14.19)
No. of rotations per week	1708 (545.4)	1900 (1,275 to 2,100)
Gait speed before therapy (s)	22.16 (3.6)	23 (19.50 to 25)
Gait speed after therapy (s)	19.36 (4.23)	19 (15 to 22.5)
Bladder capacity before therapy (ml)	193.2 (64.4)	200 (165 to 250)
Bladder capacity after therapy (ml)	257.4 (61.01)	250 (200 to 300)
Koff scale before therapy (percentage)	35.90 (21.87)	30.95 (23.48 to 45.45)
Koff scale after therapy (percentage)	19.58 (15.19)	16.67 (9.09 to 24.24)
No. of urinary leak episodes before therapy	6.82 (4.3)	7 (4 to 9.25)
No. of urinary leak episodes after therapy	3.11 (2.97)	3 (0.75 to 4.25)

TABLE 2 Spearman rank correlation matrix between 20-meter gait speed (seconds) and rotations per week.

p-values			
	Gait speed (BT)	Gait speed (AT)	Rotations per week
Gait speed (BT)		<0.001	0.051
Gait speed (AT)	<0.001		<0.001
Rotations per week	0.051	<0.001	

Correlation matrix ρ			
	Gait speed (BT)	Gait speed (AT)	Rotations per week
Gait speed (BT)	1	0.877	−0.395
Gait speed (AT)	0.877	1	−0.635
Rotations per week	−0.395	−0.635	1

Correlation matrix ρ confidence intervals			
	Gait speed (BT)	Gait speed (AT)	Rotations per week
Gait speed (BT)		0.7313 to 0.9460	−0.6900 to 0.01241
Gait speed (AT)	0.7313 to 0.9460		−0.8273 to −0.3088
Rotations per week	−0.6900 to 0.01241	−0.8273 to −0.3088	

BT, before therapy; AT, after therapy. The bold values in the table are p-values.

The best achievement of applying the GIGER MD technique was reducing the number of urinary incontinence episodes by 55.57%. The incontinence rate (leakage episodes/per day) shows considerable improvement in most children (Figure 1C; Table 1). This cannot be attributed to any single variable separately but probably to the combined effect of all variables, which had different recovery rates. Our sample size was inadequate for the non-parametric equivalent of the ANOVA test (Scheirer–Ray–Hare). This is a limitation of our

TABLE 3 Spearman rank correlation matrix between voiding bladder capacity, Koff scale deviation, urinary incontinence per day (UI).

<i>p</i> -values			
	Rotations per week	Capacity	Koff score
Rotations per week		0.004	0.001
Capacity	0.004		<0.001
Koff score	0.001	<0.001	

Correlation matrix ρ			
	Rotations per week	Capacity	Koff score
Gait speed (BT)	1	0.458	−0.515
Gait speed (AT)	0.458	1	−0.660
Rotations per week	−0.515	−0.660	1

Correlation matrix ρ confidence intervals			
	Rotations per week	Capacity	Koff score
Gait speed (BT)		0.1528 to 0.6838	−0.7212 to −0.2242
Gait speed (AT)	0.1528 to 0.6838		−0.8125 to −0.4238
Rotations per week	−0.7212 to −0.2242	−0.8125 to −0.4238	

BT, before therapy; AT, after therapy. The bold values in the table are *p*-values.

study. We strongly encourage future research on this subject. However, 1/6 had deterioration of several urinary incontinence episodes, while 5/36 children showed no improvement despite 500–2,300 rotations.

The second-best achievement was the improvement of bladder capacity. The moderate positive correlation between bladder capacity and gait speed means that the more rotations in the Giger MD a child makes, the more the bladder capacity (in milliliters) will increase significantly. The moderate negative correlation between the Koff scale and gait speed means that the more rotations in the Giger MD a child makes, the more the Koff scale of bladder size will correspond to the values for age (measured as a percentage) (Figure 1B). The moderate correlation between gait speed and bladder capacity/Koff scale is due to the different recovery rates between these two variables. Gait speed recovery vs. bladder capacity/Koff scale shows a faster recovery rate of bladder capacity compared to gait speed. 7/36 children had no improvement despite exerting themselves on rotations (500–2,300 rotations). There was no deterioration in bladder capacity and Koff scale. Most of them had surgical anorectal interventions or congenital anomalies in that area.

The third-best is the improvement of gait speed. The strong negative correlation between rotations per week and gait speed means that the more rotations in the Giger MD a child makes, the faster the 20-meter track will be walked by a child (Figures 1D, 2). There were only 5/25 children with no improvement in gait speed. There was no deterioration in gait speed. Most had surgical treatment, congenital anomalies, and hemiparesis in that area.

Conclusion/implications

Applying the GIGER MD method, achieving a satisfactory improvement in urinary incontinence episodes, gait speed, and bladder capacity in patients with neurogenic bladder is possible. The method is harmless, psychologically acceptable for the patient, and can be applied with other non-surgical and surgical procedures. This is the first study using a biofeedback (GIGER MD) device in patients with neurogenic bladder. Further studies are needed to evaluate the long-term effect of the biofeedback (GIGER MD) device on the neurogenic bladder. According to our experience so far, it takes 3–6 months of regular exercise and further maintenance exercise 2 times a month or more often, depending on the possibilities.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Committee of the University Hospital Centre “Sisters of Charity.” Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin.

Author contributions

AC-R, DMil, and VM: conceptualization. AC-R and VM: methodology. DT: software. DMil, GR, and VM: validation. DT and DMil: formal analysis, and writing—original draft preparation and review and editing. AC-R, DMik, GR, and VM: investigation. AC-R, DMik, and VM: resources. DMik and VM: data curation. DT: visualization. AC-R, GR, and VM: supervision. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Neuroblastoma of the lumbosacral canal in an adult: a case report and literature review

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Neuroblastoma (NB) is a leading cause of death in children. It usually occurs in the adrenal gland and rarely in the spinal canal. Here, we report the case of a 48-year-old male patient with abnormal thickening of the cauda equina nerve as revealed by lumbosacral magnetic resonance imaging. The patient's main clinical manifestations were numbness and pain in both lower limbs. The patient underwent surgical treatment; however, intraoperatively, an unclear border was observed between the cauda equina nerve and the tumor; therefore, the tumor was not forcibly excised. The postoperative pathological results were reported as NB. The disease known as NB, which is extremely rare. We believe that a pathological biopsy is extremely vital for diagnosing NB, and aggressive post-operative radio-chemotherapy could potentially prolong the patient's survival time.

KEYWORDS

neuroblastoma, lumbosacral canal, surgery, tumor, neurological deficits

1. Introduction

Neuroblastoma (NB) is the most common extracranial solid tumor in children, with a higher prevalence in males than in females and a higher mortality rate among younger children (1, 2). NB comprises approximately 9% of childhood cancers and is rare in adults (3–7). Compared to children, most adults are diagnosed when the cancer has already metastasized (8). NBs can occur throughout the sympathetic nervous system, most commonly in the adrenal gland (47%), abdominal/retroperitoneal region (24%), and sympathetic ganglia (9). Nevertheless, it is rare in other regions of the sympathetic nervous system (10), particularly NBs originating in the adult adrenal medulla, which are extremely rare (11, 12). Here, we report a rare case of an adult patient with spinal NB.

2. Case description

The patient was a 48-year-old male (height, 160 cm; weight, 49 kg) who was not engaged in heavy physical work and had a history of smoking for 10 years, with an average of one pack daily. He had no history of alcohol consumption. No obvious causes of eyelid droop and blurred vision were found 1 year before admission to our hospital, and the neostigmine test was positive. Titin and RyR antibody statuses were positive, and his local hospital diagnosed him with myasthenia gravis. Brombistigmine 60 mg was administered three times daily. The

patient reported some relief in his effectiveness; however, 3 months before admission to our hospital, his lower limb weakness had worsened and was accompanied by numbness; accordingly, he was referred to our hospital for treatment. Physical examination showed that the patient had clear consciousness, fluent speech, and normal memory and orientation; furthermore, bilateral gastrocnemius tenderness was present, muscle strength was grade 5 for both upper limbs, grade 5 for the proximal left lower limb, and grade 4 for the right lower limb, and grades 4 and 3 for the back and plantar flexion, respectively. The tendon reflexes of both upper limbs were normal; the knee-tendon reflex of both lower limbs presented hyperreflexia. Ankle reflex decreased, the lateral side of both lower legs and the superficial sensation of the dorsum of the foot decreased, deep tenderness beside the spinous process of the L4-5 intervertebral space was accompanied by lower limb radial pain, and the deep sensation below both iliac arteries was slightly decreased.

3. Diagnostic assessment

The finger-nose and heel-knee-shin test results were normal, and a bilateral positive Babinski sign was observed. Based on the patient's symptoms, including lower limb weakness and numbness, we speculated that the patient may have malignancy, infections, or cauda equina syndrome (13, 14). Therefore, we suggested that he undergo a magnetic resonance imaging (MRI) of the lumbosacral region to observe if any lesions exist within the spinal canal. Lumbosacral MRI showed abnormal thickening of the cauda equina nerve in the spinal canal at the L5-S2 level (Figure 1), and the shape and location of the masses were relatively rare. Due to the rapid progression of the patient's condition, malignancy in the lumbosacral region was comparable, although the possibility of central nervous system infection cannot be ruled out. Therefore, it was recommended that the patient undergo positron emission tomography/computed tomography (PET/CT) and have his cerebrospinal fluid collected. PET/CT showed that the cauda equina in the spinal canal was thickened, and multiple linear radioactive concentrations were present (Figure 2). Cerebrospinal fluid examination revealed a monocyte reaction and heterologous cells were positive. To rule out the possibility of tumor metastasis in the intracranial and other parts of the spinal canal, we recommended

that the patient undergo an MRI of the cranium, cervical, and thoracic spine; the results revealed no obvious abnormalities. Subsequently, the patient was transferred to the neurosurgery department for tumor removal.

The patient was placed in a prone position, and an L5-S2 skin incision was made on the spinous process; the subcutaneous and fascia were cut layer-by-layer, the muscles were separated and pulled on both sides, and the spinous process and vertebral lamina were completely ground down through piezosurgery. After the dura mater and arachnoid membrane were excised, the tumors were mainly located at the S1 and S2 levels and originated in the cauda equina. Approximately two-thirds of the cauda equina nerve in the sacrum showed tumor growth with different thicknesses, yellow-white color, soft texture, and rich blood supply. The larger tumor on the right side was removed; however, no obvious boundary was observed between the tumor and nerve root, and complete removal was not achieved. Finally, the tumor tissue (approximately $2.5 \times 0.3 \times 0.3$ cm in size) was removed and sent for pathological examination. Other tumors were small, and the border with the nerve root was unclear; therefore, they were not treated forcibly. After careful hemostasis, they were returned to the spinal processes of the vertebral lamina (Figure 3).

Pathological examination showed the sheet distribution of cells, moderate atypia, eosinophilic cytoplasm, oval cells, nuclear staining, and some visible nucleoli; however, no clear necrosis was found (Figure 4). Immunohistochemical investigations suggested that the biopsy tissue cells expressed CK (–), Ki-67 (+30%), TTF-1 (–), Syn (+), CgA (–), CD3 (T cell +), CD20(scattered B cell +), CD56 (+), CD99 (partial +), NeuN (–), MAP-2 (+), GFAP (–), Nestin (–), NF (–), β -catenin (+), NSE (+), C-myc (–), p53 (–), and Olig-2 (individual cells +). Based on the histopathological pattern, the tumor was diagnosed as NB, World Health Organization grade IV. The multidisciplinary consultation suggested that whole central radiotherapy combined with chemotherapy (cyclophosphamide + topotecan + doxorubicin + vincristine + cisplatin + etoposide) should be performed. At discharge, the patient's general condition was acceptable. The patient complained that the symptoms of weakness in both lower limbs were slightly worse than those at the time of admission and accompanied by pain in both lower limbs. The incision on the back of the waist healed well postoperatively. Physical examination revealed that the muscle strength of both upper limbs was grade 5. The proximal and distal

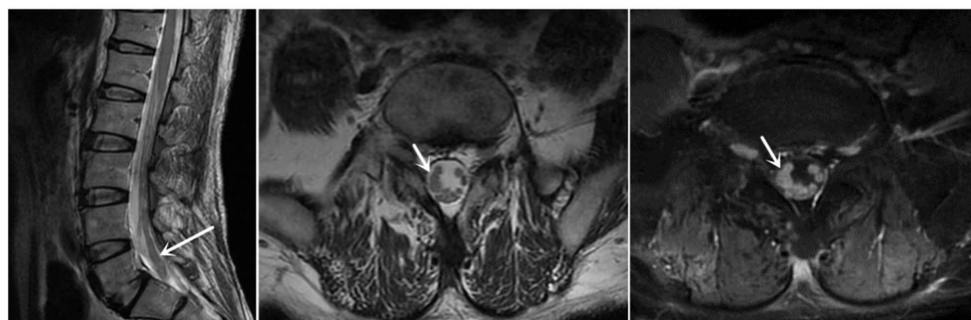


FIGURE 1

Sagittal and axial MRI revealed that the cauda equina was thickened, and enhanced MRI revealed that the cauda equina was significantly enhanced (at the white arrow). MRI, magnetic resonance imaging.



FIGURE 2

PET/CT indicating that the cauda equina in the spinal canal is thickened. SUVmax (Standardized Uptake Value): 2.7. PET/CT, positron emission tomography/computed tomography.

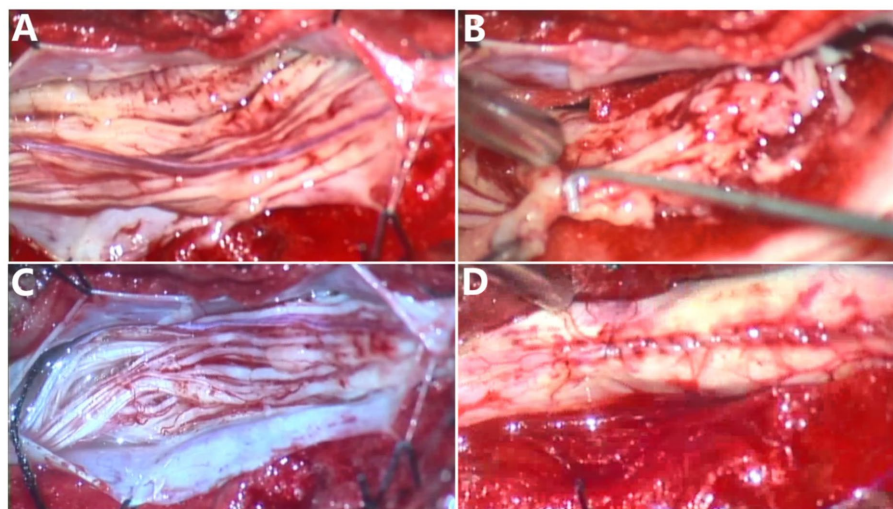


FIGURE 3

(A) The cauda equina nerve is surrounded by tumors, yellow-white, soft, and rich in blood supply. (B) Blunt stripping of the tumor and cauda equina nerve. (C) Sufficient hemostasis after biopsy. (D) Suture of the dura mater.

muscle strength of the left and right lower limbs were grade 4. Bilateral Pap signs were negative. Late in the treatment, the patient could not tolerate the radiotherapy and chemotherapy due to severe bone marrow suppression and refused further immunotherapy attempts, such as anti-gd2. After 8 months of follow-up, he died of a severe pulmonary infection. His total survival time was 22 months.

4. Discussion

Here, we summarize the most relevant origins, genetic and chromosomal alterations, clinical manifestations, and management of NB.

4.1. Origins and genetic alterations

4.1.1. Origins

A recently detailed review suggested that adrenal chromaffin cells and sympathetic neurons are reliable cell sources for NB (15). Moreover, neural crest cells are a source of NB cells (16). In vertebrates, the neural crest is a transient cell group that produces various other

cell groups under the control of a complex gene regulatory network (17). Because NBs mainly occur in the adrenal gland, sympathetic adrenal progenitor cells are considered the source of NBs. Furthermore, because primary NB occurs in the paravertebral sympathetic ganglia in addition to the adrenal gland, Schwann cell precursors are considered one of the origins of NB (15).

4.1.2. Genetic alterations

The DNA index (DI) is used to express DNA content. Typically, the DI of diploid cells is 1.0; when the DI >1.0, hyperdiploidy is considered present. Additionally, the DNA content of tumor cells is related to the pathogenesis of NB; in children with NB aged < 18 months, “patients with a DI > 1.0 had a lower tumor stage and better prognosis than those with a DI of 1.0” (18).

4.1.3. Chromosomal alterations

Pugh et al. sequenced genomic DNA samples from 240 high-risk NBs and found that chromosome changes were the most common (19). Segmental chromosomal aberrations associated with poor prognosis included *MYCN* amplification, 17q gain, 11q loss, and 1p36 loss (20). *MYCN* and *let-7* miRNA families have recently been shown to be closely related (21); *let-7* miRNAs play essential roles in inhibiting tumor

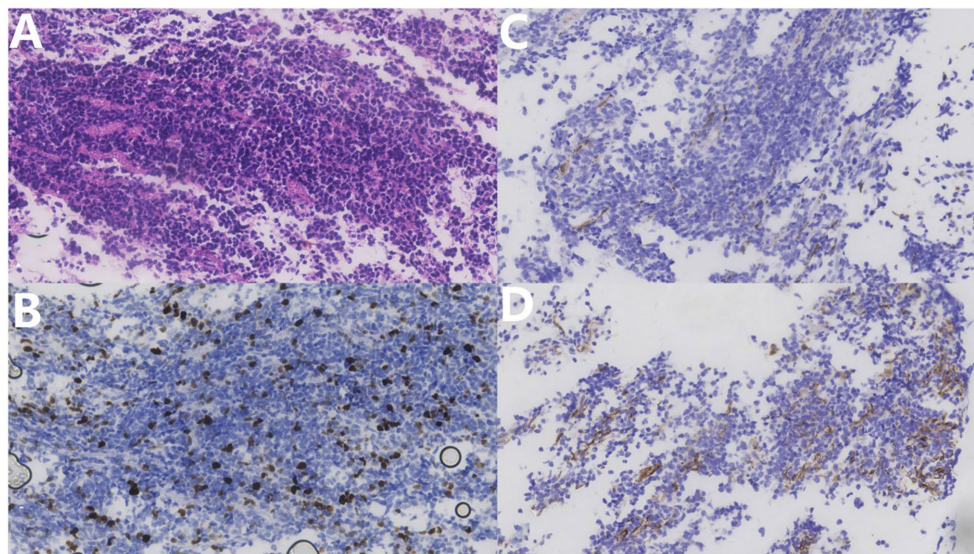


FIGURE 4

(A) Hematoxylin–eosin stain (x400) shows tumor cell sheet distribution, moderate atypia, eosinophilic cytoplasm, oval cells, nuclear staining, some visible nucleoli, and no clear necrosis. (B) Ki67 immunohistochemical staining (x400) shows approximately 30% positive rate. (C) NF immunohistochemical staining (x400). (D) NFD Nestin immunohistochemical staining (x400) shows a partial positive rate.

growth and development. Power et al. believed that the expansion of *MYCN* competitively inhibits *let-7* miRNA, weakening its tumor inhibition function (22). This hypothesis may explain why *MYCN* amplification is associated with advanced disease, rapid tumor progression, and poor prognosis (23). Regarding 17q gain, six of the 14 samples showed an unbalanced gain of one to three additional copies of 17q (24). Moreover, *MYCN* overexpression may promote an increase in the 17q chromosome. Therefore, an increase in 17q is associated with stronger tumor invasiveness, which is usually used as a genetic predictor of patient prognosis (25, 26). Approximately 30% of NB cases have 11q deletion. *MYCN* amplification and 11q deletion are the most relevant genetic markers of high-risk tumors (27). Moreover, 11q deletion, *MYCN* amplification, and tumor ploidy are the only NB markers used to determine treatment plans (28). Finally, 1p encodes one or more NB tumor suppressor genes; the most commonly missing region is located in 1p36 (29, 30).

4.2. Clinical manifestation

Posterior mediastinal NBs usually form a mass outside the dura mater. Approximately 10–15% of the tumor tissue invades the spinal canal, infiltrating the intervertebral foramen with or without spinal cord compression (31, 32). According to the degree of spinal cord compression, 7%–10% of patients may have back pain, motor disorders, sphincter dysfunction, and sensory disorders (33, 34). More than half of these patients experience permanent sequelae, which are more common in young patients (35, 36).

4.3. Management

Early decompression of the spinal cord through neurosurgery can prevent irreversible neurological changes (37, 38). Most patients who

underwent thoracic surgery and neurosurgery combined approach had complete subsidence postoperatively; therefore, this method may be safe and effective for treating mediastinal and intraspinal NB (39). However, laminectomy should be considered carefully because some patients present spinal deformities postoperatively (40, 41). Although spinal braces have become popular postoperatively, their impact remains unclear. For instance, they may delay the occurrence of spinal deformities rather than reduce them (42). Therefore, chemotherapy is the first choice, particularly in young children, for reducing the long-term sequelae of laminectomy or spinal radiation. Emergency neurosurgical decompression is only performed in the case of neuro-progression during chemotherapy (31, 43). However, in 30% of patients who received chemotherapy, neurological function did not improve and even showed signs of deterioration (43, 44). Optimal treatment for patients with epidural compression remains controversial. In some studies (37), patients receiving chemotherapy did not require further neurosurgical intervention or radiotherapy to relieve secondary compression. However, the efficacy of various treatment methods has been evaluated, and the combination of surgery and radiotherapy was associated with the greatest functional improvement (45). Long before chemotherapy was proven effective, decompression neurosurgery and radiotherapy were used to treat symptomatic spinal cord injury (46). However, 57% of children receiving radiotherapy had radiation-induced spinal deformities (47). Additionally, more severe deformities are associated with an increased radiation dose, longer follow-up time, and younger age. Therefore, radiotherapy is rarely used currently (6, 35). Furthermore, dexamethasone in spinal cord compression has been demonstrated to reduce edema, inhibit inflammatory reactions, stabilize vascular membranes, and delay the occurrence of nerve function defects (48). Some studies have shown that moderate-to-high doses of dexamethasone can be recommended for patients with significant neurological dysfunction (49). Currently, no consensus exists on the best treatment strategy for intraspinal NB (50, 51).

Krol and Horten reported only a case of NB with primary cauda equina nerve in 1980 (52). Because of the rapid progression of NB and its variable location, the atypical clinical symptoms lead to the difficulty of initial accurate diagnosis. Similar to this case, 16% of adults are misdiagnosed during their first visit, resulting in a delay in receiving appropriate treatment (53). Failure to correctly diagnose may be due to the rare incidence of NB, rare MRI scan performance, and atypical clinical symptoms. The case we reported started with numbness and weakness in the lower limbs, which was consistent with the growth site of the tumor. The MRI scan of this case showed thickening of the cauda equina roots, an inhomogeneous slightly high signal in T1WI and T2WI, and no obvious abnormality in the pressure-fat image. The cauda equina was unevenly and moderately enhanced on the enhanced scan, and its signal was coarse on the axial scan. Although the MRI scan was typical of NB, differentials for tumors in the cauda equina included the following: schwannoma (the tumor is mostly regular round-like and has a clear boundary with the cauda equina nerve); lipoma (patients with spinal cord tethered cord syndrome have filum terminale steatosis and sacral lipoma, and MRI shows thickening of the cauda equina, but MRI lipogram conducive to exclude); lymphoma (would show homogeneous enhancement in MRI scan, and inclined to invade the surrounding vertebral body); and metastatic tumors (the MRI appearance of metastatic tumors may be similar to that of NB; however, they commonly destroy the vertebral bodies and accessories and have primary lesions). The MRI manifestations of this case were specific, and the tumor growth mode differed from that of the spinal cord NB in previous reports. Commonly, NB causes spinal cord injury mostly due to the invasion of the tumor into the spinal canal through the intervertebral foramen, resulting in compressive damage to the spinal cord (37). In this case, it originated from the cauda equina, which could be observed using MRI enhancement scanning that the involved cauda equina was strengthened as a whole without a clear boundary. Intraoperatively, we found that the boundary between the tumor tissue and cauda equina nerves was blurred.

This surgical procedure had the following advantages: intraoperatively, it was observed that many cauda equina nerves in the sacral canal adhered closely to the tumor. Considering the patient's postoperative quality of life, no forced resection was performed; therefore, no significant damage was caused to the cauda equina nerves. The limitation is that the tumor may not have been completely excised; therefore, future recurrence is possible. A study conducted by Hung et al. reported on the tentative use of chemotherapy drugs, including carboplatin, etoposide, cyclophosphamide, and doxorubicin for neoadjuvant chemotherapy in adult male patients with NB; reexamination showed that the patients' tumors shrank by approximately 17% (54). Unfortunately, this patient did not receive chemotherapy. Therefore, we highly recommend that patients undergo chemotherapy and regular follow-up to monitor tumor growth after biopsies.

5. Conclusion

Adult NB originates from the adrenal medulla, which is extremely rare. MR imaging and clinical symptoms may not show obvious features; therefore, a pathological biopsy may be necessary for

diagnosis. Due to the overall poor prognosis of this disease, and the lack of clear boundaries between tumor tissue and the adrenal medulla, surgical resection can be challenging. However, aggressive chemotherapy followed by maintenance therapy may be beneficial in prolonging patient survival.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Chinese PLA General Hospital and don't contain identifiable human images. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

QJ and GG wrote the main manuscript text. YL, GS, and HC prepared Figures 1–3. HG prepared Figure 4 and provided interpretations of the pathological results and made revisions to the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Percutaneous uniportal full-endoscopic surgery for treating symptomatic lumbar facet joint cysts under local anesthesia combined with monitored anesthesia care: a preliminary report of eight cases with at least 1 year follow-up

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Background: Lumbar facet joint cysts (FJC) are a relatively rare clinical pathology that can result in radiculopathy or neurogenic claudication. Various treatments such as percutaneous aspiration and surgery have been reported to have good clinical outcomes. However, few clinical studies have aimed to treat symptomatic lumbar FJCs by using uniportal full-endoscopic (UFE) surgery. This study aimed to investigate the preliminary clinical outcomes of UFE surgery for the treatment of lumbar FJCs under local anesthesia combined with monitored anesthesia care (MAC).

Methods: Eight patients (five males and three females) with symptomatic lumbar FJCs who underwent UFE surgery under local and MAC anesthesia were enrolled in this study between January 2018 and April 2022. The clinical characteristics, radiological features, operative information, visual analog scale (VAS) score, Oswestry disability index (ODI), and overall outcome rating based on the modified MacNab criteria were retrospectively analyzed.

Results: Of the eight patients, four underwent a transforaminal approach and four underwent an interlaminar approach. Postoperatively, the mean VAS score for leg pain decreased from 6.1 before surgery to 0.6 after surgery, and the ODI decreased from 74.5% to 14.7%. All patients were followed up for more than 1 year, and the good-to-excellent rate based on the modified MacNab criteria remained 100% at the last follow-up. No complications occurred during the follow-up period.

Conclusion: Lumbar FJCs can cause severe radiating leg pain and/or neurogenic claudication due to the dural sac compression and nerve roots. As an alternative treatment, UFE decompression under local and MAC anesthesia may provide effective clinical outcomes for symptomatic lumbar FJCs.

KEYWORDS

uniportal endoscopy, full endoscopy, lumbar facet joint cyst, interlaminar approach, transforaminal approach, local anesthesia

1 Introduction

Facet joint cysts (FJC)s are estimated to affect 0.65%–6.4% of the population and are commonly found in the lumbar spine but rarely in the cervical or thoracic spine (1–5). The pathogenesis of FJC)s remains unknown; however, FJC)s are associated with spinal instability or degenerative spondylolisthesis (6, 7). Lumbar FJC)s can be symptomatic because of compression of the spinal cord or nerve roots, resulting in radiculopathy, back pain, cauda equina syndrome, or neurological claudication, especially in cases of hematoma of the cysts, which occurs in approximately 3% of synovial cysts (8–11).

Image-guided intraarticular aspiration, image-guided cyst rupture, image-guided epidural steroid injection, laminotomy, and decompression by microsurgical or traditional open techniques have been reported to be effective in treating symptomatic lumbar FJC)s (12–16). Recently, uniportal full endoscopy (UFE), a minimally invasive technique, has been widely applied to treat lumbar disc herniation, lumbar spinal stenosis, and cervical spondylopathy (17, 18). Moreover, the UFE technique has also been used for the treatment of lumbar FJC)s, showing satisfactory clinical and radiological outcomes (19, 20). However, only a few studies have reported on the UFE technique for treating lumbar FJC)s under local anesthesia (21, 22). Therefore, this study aimed to investigate the preliminary clinical outcomes of the UFE technique for the treatment of symptomatic lumbar FJC)s under local anesthesia combined with monitored anesthesia care (MAC).

2 Methods

2.1 Subjects

This retrospective study was approved by the Ethics Committee of the Beijing Friendship Hospital, Capital Medical University. Informed consent was obtained from all the participants. The medical records of patients with symptomatic lumbar FJC)s who were hospitalized at our spine center and underwent surgical resection using the UFE technique by one senior spine surgeon between January 2018 and April 2022 were retrospectively reviewed. The inclusion criteria were as follows: (1) neurogenic claudication or radiating leg pain with associated neurological signs; (2) compression by FJC)s confirmed on the lumbar MRI; and (3) failure of conservative treatment for at least 3 months. Three patients were excluded due to $\geq$ II degree lumbar spondylolisthesis, a prior history of surgery at the surgical level, and incomplete medical records.

2.2 Surgical technique

All procedures were performed under local anesthesia, MAC, and sufentanil administration. All procedures were performed with endoscopic techniques through an interlaminar or transforaminal approach. The surgical approach for UFE was decided based on the anatomical locations of the FJC)s. The interlaminar approach was performed in the other four patients because the FJC)s were located around the caudal half of the medial side of the facet, and the transforaminal approach was used in four patients because the FJC)s were located around the rostral half of the medial side of the facet.

Patients who underwent UFE surgery using the interlaminar approach were placed in the prone position on a radiolucent table. An 18-gauge spinal needle was inserted into the posterior ligamentum flavum, and the needle was confirmed to be located at the midpoint of the interlaminar space of the fluoroscope. The guidewire, obturator, working cannula, endoscopic trephine, and endoscopic system were then inserted sequentially. The ipsilateral upper lamina, inferior articular process, and superior articular process were partially removed using a trephine or Kerrison punch to adequately expose the facet cyst. After opening the ligamentum flavum, the facet cysts were detected and removed using Kerrison punches or disc forceps. Surgeries were concluded when the complete resolution of dura and nerve root compression had been obtained with non-evidence of the residual cyst wall.

Patients who underwent UFE using the transforaminal approach were laterally positioned on a radiolucent table. An 18-gauge spinal needle was inserted into the lateral aspect of the superior articular facet, as confirmed by fluoroscopy. The guidewire, obturator, working cannula, endoscopic trephine, and endoscopic system were inserted sequentially. The superior articular process was partially resected using a trephine. The facet cyst was resected using disc forceps. Surgeries were concluded when the complete resolution of dura and nerve root compression had been obtained with non-evidence of the residual cyst wall (Figure 1).

2.3 Demographic data collection and outcome assessment

Demographic data including sex, age, surgical level, operation time, estimated blood loss, duration of postoperative hospitalization, and complications were systematically collected. Visual analog scale (VAS) scores for leg pain were evaluated preoperatively, immediately postoperatively, and at the last follow-up (at least 1 year). Oswestry disability index (ODI) scores were assessed preoperatively and at the last follow-up. The modified MacNab criteria were recorded at the last follow-up (23). Computed tomography (CT) of the lumbar spine was performed preoperatively and 1 day postoperatively. Magnetic resonance imaging (MRI) of the lumbar spine was performed before surgery and at 3 months follow-up.

2.4 Statistical analysis

Categorical variables were grouped and presented as numerical values, whereas continuous data were presented as mean values. The Wilcoxon signed-rank test was used to compare VAS and ODI scores at the preoperative, postoperative, and last follow-up. Statistical significance was set at a p -value of <0.05 . All data analyses were performed using SPSS v25.0 software (IBM Corp., Armonk, NY, United States).

3 Results

3.1 Characteristics of patients and facet cysts

Eight patients with lumbar FJC)s were enrolled in this study, five male and three female patients. The mean age was 53.9 years (range 28–72 years). All eight patients had radiating leg pain as the chief

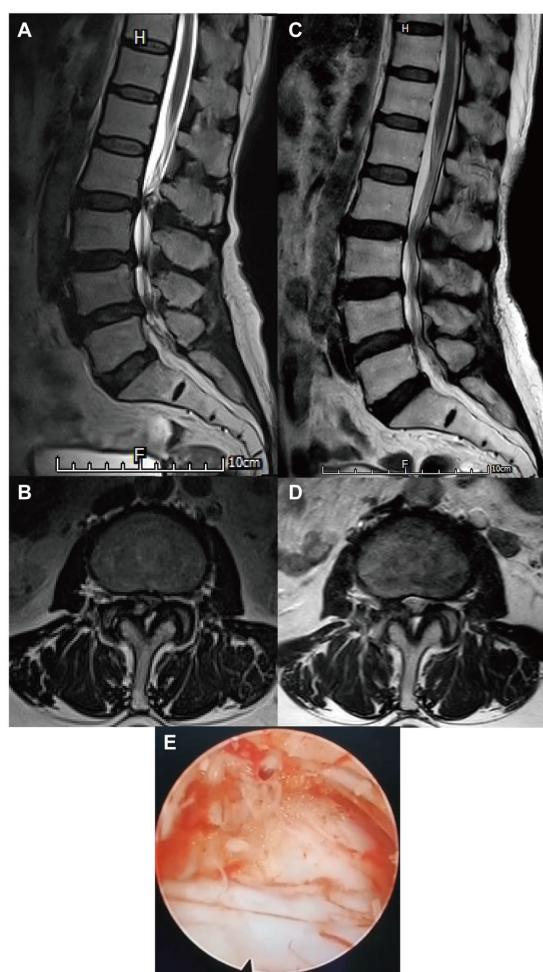


FIGURE 1
Radiological images of a patient with lumbar facet joint cyst (FJC) who underwent uniportal full-endoscopic (UFE) surgery through a transforaminal approach. (A,B) Preoperative magnetic resonance imaging (MRI) of the lumbar spine revealed one cyst located at the right facet joint at the L2-3 level. (C,D) A postoperative MRI of the lumbar spine showed that the FJC was completely removed. (E) Endoscopic view of the FJC during the UFE surgery.

complaint, of whom two had neurogenic claudication. Based on preoperative MRI of the lumbar spine, most facet cysts (7/8, 72.5%) were located at the L4-5 level, and only one cyst was at the L2-3 level. The mean duration of operation was 72.0 min (range 60–90 min), the mean estimated blood loss was 31.2 mL (range 20–50 mL), and the length of postoperative stay was 1.5 days (range 1–3 days) (Table 1).

3.2 Surgical outcomes

All patients were followed up for at least 12 months (range 12–23 months). The mean VAS score for leg pain significantly improved from 6.1 (range 5–7) to 0.6 (range 0–2) immediately after surgery ($p = 0.010$) and further decreased to 0.5 (range 0–2) at the last follow-up ($p = 0.010$). The mean ODI score at the last follow-up significantly improved from 74.5% (range 66%–80%) to 14.7% (range 8%–25%) compared to the preoperative score ($p = 0.012$). Based on the modified MacNab criteria at the last

follow-up, excellent results were obtained in six (75%) patients and good results in two (25%) patients. No perioperative complications were observed, including dural tears, neurologic deterioration, or hematoma compression, and no spinal instability or reoperation was performed during follow-up. No residual cyst was detected by postoperative CT or MRI (Table 2).

4 Discussion

Percutaneous aspiration, rupture, corticosteroid injection, and surgery were effective in patients with symptomatic lumbar FJCs who failed to respond to conservative therapy. Kim et al. (14) evaluated the clinical outcomes of a three-stage minimally invasive percutaneous technique for lumbar intraspinal synovial cysts and found that endoscopic superior facetectomy resulted in no recurrence within the 3 years follow-up. One meta-analysis revealed no significant differences in outcome or complication rates between microscopic and endoscopic resection for lumbar FJCs (13). Another meta-analysis showed that full endoscopy could achieve 90% satisfactory outcomes with low rates of adverse events (<2%) better than open and minimally invasive surgeries (24). One prospective multicenter study by Tacconi et al. (20) reported the clinical outcomes of full-endoscopic surgery for lumbar FJCs. At a median follow-up of 15 months, 89% of patients were pain-free or improved, showing outcomes comparable to those of open or tubular techniques. Hellinger et al. (25) analyzed 2 years follow-up outcomes of 48 patients who were treated with endoscopic removal of extradural cysts; excellent or good results based on the MacNab criteria were obtained in 37 out of 48 (77.1%) patients. Hagan et al. (22) introduced awake transforaminal endoscopic decompression surgery for the treatment of lumbar FJCs in patients with lumbar radiculopathy, and the VAS score for leg pain improved significantly without complications, readmission, or symptom recurrence during a 2 years follow-up period. In this study, the VAS score for leg pain and ODI score improved after UFE surgery. The overall excellent-good rate of the modified MacNab criteria was 100% without any complications or recurrence. These findings support the satisfactory outcomes achieved using the UFE technique in patients with symptomatic lumbar FJCs. Moreover, the UFE approach was chosen mainly based on the location of the lumbar FJCs relative to the facet joints. When the FJCs were located around the rostral half of the medial side of the facet, the transforaminal approach was preferred; otherwise, the interlaminar approach was considered (21). In addition, the choice of surgical approach should consider the operating habits of the surgeon and the anatomical characteristics of the patient's lumbar spine.

Whether fusion is needed has also been discussed in patients with lumbar FJCs undergoing decompressive operation (26). The NeuroSpine Surgery Research Group proposed a classification system (grades 1–5) for lumbar FJCs based on the percentage of the vertebral canal occupied by the cyst on MRI and the degree of spondylolisthesis in the involved segment. Patients with grade 4 and 5 FJCs show a greater risk of recurrence following decompression alone, and stabilization of the involved segments should be considered for initial decompressive surgery in these patients (27, 28). Thompson et al. (29) reported that the revision

TABLE 1 Patients' information.

Patient	Sex	Age	Symptom	Facet cyst location	Approach	Operation duration (min)	Estimated blood loss (mL)	Length of postoperative stay (days)
1	Male	63	Radiculopathy	Left L4-5	Transforaminal	60	25	1
2	Male	45	Claudication + Radiculopathy	Left L4-5	Interlaminar	68	20	1
3	Female	62	Radiculopathy	Left L4-5	Transforaminal	72	30	2
4	Male	39	Radiculopathy	Left L4-5	Transforaminal	72	25	2
5	Male	28	Claudication + Radiculopathy	Left L4-5	Interlaminar	65	30	1
6	Female	72	Radiculopathy	Right L2-3	Interlaminar	90	20	2
7	Female	57	Radiculopathy	Right L4-5	Transforaminal	65	50	2
8	Male	65	Radiculopathy	Left L4-5	Interlaminar	84	50	1

TABLE 2 Surgical outcomes.

Patient	VAS for leg pain			ODI		MacNab	Follow-up (month)	Complication
	Preoperative	Postoperative immediately	Last follow-up	Preoperative	Last follow-up			
1	7	2	2	75	25	Good	23	N/A
2	6	1	0	68	12	Excellent	20	N/A
3	5	0	0	78	8	Excellent	14	N/A
4	7	2	2	80	30	Good	16	N/A
5	7	0	0	66	12	Excellent	18	N/A
6	6	0	0	71	16	Excellent	12	N/A
7	5	0	0	78	8	Excellent	12	N/A
8	6	0	0	80	15	Excellent	12	N/A

VAS, visual analog scale; ODI, Oswestry disability index.

rate was as high as 20.4% in patients who received limited decompression for lumbar FJCs and found that a facet angle $>45^\circ$ at L4-5 was associated with the risk of failure of primary decompression. Page et al. (30) reported a predictive model for lumbar synovial cyst recurrence following decompression without fusion and found some predictive factors of recurrence, including a facet inclination angle of $>45^\circ$, canal stenosis of $>50\%$, T2 joint space hyperintensity, and the presence of grade I spondylolisthesis. One systematic review and meta-analysis showed that decompression combined with fusion was associated with better results in terms of lower postoperative back pain and cyst recurrence compared with decompression alone; however, there were no differences in the reoperation and complication rates (31). None of the patients in this study experienced recurrence or reoperation during the follow-up period. This may be associated with the advantage of the UFE technique of minimal trauma to the paraspinal muscles and the posterior ligamentous complex of the lumbar spine (32).

The current study had some limitations. First, it was a retrospective study with a relatively small sample size. Further prospective studies with larger sample sizes are warranted to verify the efficacy of UFE. In addition, the minimum 1 year follow-up was relatively short to assess recurrence and reoperation. A continuous long-term follow-up of these patients is needed.

Lumbar FJCs can cause severe radiating leg pain and/or neurogenic claudication due to the compression of the dural sac and nerve root. The decompression accomplished by the UFE technique under local and MAC anesthesia may provide effective clinical outcomes for symptomatic lumbar FJCs and could be an alternative treatment for symptomatic lumbar FJCs.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ethics Committee of Beijing Friendship Hospital, Capital Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) for the publication

of any potentially identifiable images or data included in this article.

Author contributions

HT: Conceptualization, Funding acquisition, Writing – original draft. LY: Investigation, Writing – original draft. XL: Supervision, Writing – original draft. YY: Supervision, Writing – original draft. BZ: Conceptualization, Funding acquisition, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Classification of and individual treatment strategies for complex tethered cord syndrome

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Objective: To study the classification, diagnosis, and treatment strategies of complex tethered cord syndrome (C-TCS) on the basis of the patients' clinical symptoms, imaging findings, and therapeutic schedule.

Methods: The clinical data of 126 patients with C-TCS admitted to our department from January 2015 to December 2020 were retrospectively analyzed. Classification criteria for C-TCS were established by analyzing the causes of C-TCS. Different surgical strategies were adopted for different types of C-TCS. The Kirolos grading, visual analogue scale (VAS), critical muscle strength, and Japanese Orthopaedic Association (JOA) scores were used to evaluate the surgical outcomes and explore individualized diagnosis and treatment strategies for C-TCS.

Results: C-TCS was usually attributable to three or more types of tether-causing factors. The disease mechanisms could be categorized as pathological thickening and lipomatosis of the filum terminal (filum terminal type), arachnoid adhesion (arachnoid type), spina bifida with lipomyelomeningocele/meningocele (cele type), spinal lipoma (lipoma type), spinal deformity (bone type), and diastomyelia malformation (diastomyelia type). Patients with different subtypes showed complex and varied symptoms and required individualized treatment strategies.

Conclusion: Since C-TCS is attributable to different tether-related factors, C-TCS classification can guide individualized surgical treatment strategies to ensure complete release of the tethered cord and reduce surgical complications.

KEYWORDS

complex tethered cord syndrome, classification, individual treatment, tethercausing factor, release, decompression

1 Introduction

Tethered cord syndrome (TCS) is a common disease characterized by developmental malformations of the spine and spinal cord (1, 2). Most of the cases of TCS are congenital while a few are acquired. In this study, all of the patients showed congenital developmental malformations and were newly diagnosed patients. The imaging manifestations of this disease are varied, and mainly include a low spinal cord, myelolipoma, lipomyelomeningocele/meningocele, syringomyelia, diastematomyelitis, spina bifida, scoliosis, and fur sinuses (3–6). Complex TCS (C-TCS) is accompanied by complex and varied spinal cord manifestations and nerve root adherents along with severe lumbosacral coccygeal vertebrae deformities (7). Patients with C-TCS may also show excessive lordosis or kyphosis of the spine, torsion deformation, severe spinal canal

stenosis, and other such changes that may make it almost impossible to distinguish the normal anatomical structure (8). The severe clinical symptoms, complex imaging manifestations, and disorganized anatomical structure increase the difficulty of surgical treatment (9, 10). This study retrospectively analyzed the clinical data of patients with C-TCS admitted to the Neurosurgery Department of the Seventh Medical Center of the People's Liberation Army General Hospital from January 2015 to December 2020. The clinical symptoms, imaging findings, treatment methods and other clinical characteristics of these patients were studied, and the classification and diagnosis and treatment strategies of C-TCS were summarized.

2 Patients and methods

2.1 General information

A total of 126 patients (46 males, 80 females; age, 3 months–65 years; mean age, 23 ± 2.3 years) with C-TCS were included. The study cohort included 103 cases of lower-extremity dysfunction, 109 cases of urine and bowel abnormalities, 45 cases of sexual dysfunction, 122 cases of skin abnormalities, and 37 cases of spinal deformity (Table 1). We included patients showing (1) presence of congenital TCS; (2) more than three types of thrombotic factors; and (3) worsening of symptoms in the last three years. On the other hand, we excluded (1) patients with acquired TCS; (2) patients who had undergone tethered cord-related surgery; (3) patients with two or less thrombotic factors; and (4) patients with incomplete clinical data. These patients were divided into four groups: A, B, C and D which respectively included three, four, five, and six tether-causing factors.

2.2 Clinical signs and symptoms

The main symptoms were urinary and bowel dysfunction, lower limb dysfunction, and sexual dysfunction, consistent with the theory that higher-level nerves were less damaged while lower-level nerves were inevitably damaged in this disease. The specific manifestations included frequent urination, urgent urination, weak urination, incomplete dripping, dysuria, urinary retention, urinary incontinence, dry stool, irregular defecation, difficulty defecation, fecal incontinence, paresthesia such as pain and numbness of both

lower limbs, weakness of both lower limbs, bipedal deformity, muscle atrophy and even paralysis of lower limbs, and erectile dysfunction. The main signs included the presence of lumbosacral skin masses, meat tags or skin depressions, local skin pigmentation, abnormal hair distribution, fur sinus, scoliosis, or even kyphosis or lordosis. According to JOA score, the severity of clinical manifestations of the patients was divided into mild (25 cases): 25–29 points, moderate (48 cases): 16–24 points, severe (36 cases): 10–15 points, extremely severe (17 cases): <10 points, and the distribution of the severity of clinical manifestations in the 4 groups were listed (Table 2). All patients showed varying degrees of symptom aggravation within 3 years.

2.3 Imaging manifestations

Lumbosacral vertebral MRI was performed in all patients. The main imaging manifestations included a low spinal cord, myelolipoma, lipomyelomeningocele (meningocele), syringomyelia, diastematomyelitis, spina bifida, and sacral cysts in a few patients. These common imaging abnormalities indicate that C-TCS is associated with a severe spinal cord end and nerve root adherents and significant lumbosacral coccygeal deformities, excessive lordosis, kyphosis, torsion deformation or severe spinal canal stenosis, which make it almost impossible to distinguish the normal anatomical structure. CT scans revealed the absence of lumbosacral spinous processes and lamina, formation of bone spurs within the spinal canal, abnormal free bone, spinal canal stenosis or pathological dilatation, lumbosacral coccygeal lordosis, kyphosis, lateral curvature, or torsion.

2.4 Other examinations

All patients underwent bladder residual urine ultrasonography, electromyography of both lower limbs, and urodynamic examinations to provide objective examination data for evaluating the status of patients before and after the operation.

2.5 Surgical treatment

The main causes of C-TCS include pathological thickening and lipomatosis of the filum terminal (filum terminal type), arachnoid adhesion (arachnoid type), spina bifida with lipomyelomeningocele/

TABLE 1 Basic information of the patients.

Total number of patients	126
Male	46
Female	80
Age	3 months–65 years
Mean age	23 ± 2.3 years
Lower-extremity dysfunction	103
Urine and bowel abnormalities	109
Sexual dysfunction	45
Skin abnormalities	122
Spinal deformity	37

TABLE 2 Distribution of severity of clinical manifestations in 4 groups.

	A group	B group	C group	D group	Total
Mild	18 (25.4%)	6 (16.2%)	1 (9.1%)	0	25 (19.8%)
Moderate	32 (45.1%)	12 (32.4%)	3 (27.3%)	1 (14.4%)	48 (38.1%)
Severe	15 (21.1%)	15 (40.6%)	3 (27.3%)	3 (42.8%)	36 (28.6%)
Extremely severe	6 (8.4%)	4 (10.8%)	4 (36.3%)	3 (42.8%)	17 (13.5%)
Total	71	37	11	7	126

In general, the more tether-causing factor, the more severe the clinical manifestations. There were more mild and moderate cases in group A, more moderate and severe cases in group B, more severe and extremely severe cases in group C and D, and even no mild cases in group D.

TABLE 3 The number of appearance of the tether-causing factor.

Tether-causing factor	The number of times
Filum terminal type	120
Arachnoid type	112
Cele type	78
Lipoma type	65
Bone type	34
Diastomyelia type	27

meningocele (cele type), spinal lipoma (lipoma type), spinal deformity (bone type), and diastomyelia malformation (diastomyelia type). C-TCS is usually caused by three or more thrombolytic factors. The tether-causing factors differ among patients, and the imaging findings are complex and varied. Therefore, surgical strategies should differ according to the tether-causing factors; thus, each patient requires individualized surgical treatment strategies.

2.6 Follow-up and evaluation

The Kirolos scale, visual analogue scale (VAS), muscle strength, and Japanese Orthopaedic Association (JOA) scores were used to assess the postoperative improvement in clinical symptoms and thereby evaluate the surgical effect. The follow-up period was 12–60 months. Lumbosacral vertebral MRI, residual urine ultrasound of the bladder, electromyography of both lower limbs, and urodynamics examination were performed in the follow-up assessments.

3 Results

3.1 Diagnosis and treatment strategy and surgical effect

Pathological thickening and lipomatosis of the filum terminal (filum terminal type), arachnoid adhesion (arachnoid type), spina bifida with lipomyelomeningocele/meningocele (cele type), spinal lipoma (lipoma type), spinal deformity (bone type), and diastomyelia malformation (diastomyelia type) are common tether-causing factors in TCS. However, C-TCS often manifests with three or more of these tether-causing factors, complicating the disease and greatly increasing the difficulty of surgery. The number of times which the filum terminal, arachnoid, cele,

TABLE 5 Evaluation of the degree of tethered cord release in the 4 groups with the kirolos scale.

	A group	B group	C group	D group	Total
Grade 1	67 (94.4%)	32 (86.5%)	9 (81.8%)	4 (57.1%)	112 (88.9%)
Grade 2	4 (5.6%)	5 (13.5%)	2 (18.2%)	2 (28.6%)	13 (10.3%)
Grade 3	0	0	0	1 (14.3%)	1 (0.8%)
Total	71	37	11	7	126

88.9% of patients had the degree of surgical release reaching grade 1. Group A > Group B > Group C > Group D, indicating that the more tether-causing factors, the lower proportion of patients reaching grade 1. Among the 4 groups, only 1 case in group D failed to release.

lipoma, bone, and diastomyelia types, appeared respectively was 120, 112, 78, 65, 34, and 27 (Table 3). The statistical data indicated that almost all patients showed the filum terminal-type and arachnoid-type tether-causing factors, and that C-TCS may especially present with more than four types of tether-causing factors. The greater the number of tether-causing factors, the more difficult the operation, and the presence of the bone and diastomyelia types is associated with an especially difficult operation. Individual diagnosis and treatment strategies for different tether-causing factors are shown in Table 4. The Kirolos scale (Table 5), VAS, muscle strength, and JOA scores were used to evaluate the surgical effects of patients in the early and long-term postoperative follow-up assessments, and the analysis results are shown in Table 6.

Patients with more tether-causing factors generally show more complicated conditions, greater surgical difficulty, greater surgical risk, and a higher incidence of postoperative complications. On the basis of the research data, the results of early and long-term postoperative follow-up also conform to this law. Long-term follow-up after rehabilitation treatment indicated that most patients showed improvement in symptoms, including better recovery of patients who showed improvement in the early postoperative period, improvement of postoperative stable patients in comparison with preoperative patients, and recovery of patients showing disease aggravation to preoperative levels.

3.2 Analysis of typical cases

3.2.1 Case 1

The patient in this case was a 9-year-old girl showing a lumbosacral mass with bipedal deformity for 9 years and abnormal urination for 8 years who was admitted to the hospital

TABLE 4 Individualized treatment strategies for different tether-causing factors in patients with complex tethered cord syndrome.

	Filum terminal type	Arachnoid type	Lipoma type	Bone type	Diastomyelia type	Cele type
Imaging findings	Thickening/lipomatosis	Structural disorder	Lipoma signal	Paramorphia	Double spinal cord	Lipomyelomeningocele or meningocele
Intraoperative findings	High tension	Adhesion, wrap	Surrounding the spinal cord	Spine malformation	Bone or frenulum	Extraspinal
Surgical strategy	Division	Peel	Excision	Release entrapment	Excision partition	Return the spinal canal
Findings needing attention	Distinguishing boundary	Thinning spinal cord similar to arachnoid	Block the neural substrate	Ensure the stability of the spine	Repair dural sac	Recovery structure
Expected effect	Terminal ionization	Free the spinal cord	Total or subtotal cut	Perfect spinal canal	Relieve pressure	Return the contents

TABLE 6 Evaluation of surgical results in patients with complex tethered cord syndrome.

	Early postoperative period			Long-term follow-up		
	Improved	Stable	Aggravated	Improved	Stable	Aggravated
A (71)	49 (69%)	18 (25.4%)	4 (5.6%)	60 (84.5%)	10 (14.1%)	1 (1.4%)
B (37)	23 (62.2%)	8 (21.6%)	6 (16.2%)	30 (81.1%)	5 (13.5%)	2 (5.4%)
C (11)	6 (54.5%)	3 (27.3%)	2 (18.2%)	8 (72.7%)	2 (18.2%)	1 (9.1%)
D (7)	3 (42.9%)	3 (42.9%)	1 (14.2%)	4 (57.1%)	2 (28.6%)	1 (14.3%)
Total	81 (64.3%)	32 (25.4%)	13 (10.3%)	102 (80.9%)	19 (15.1%)	5 (4%)

The analysis of long-term follow-up results showed that the improvement rate of Group A > Group B > Group C > Group D.

on June 13, 2016. The patient had shown varus deformity since childhood and underwent orthopedic surgery several times. After an early improvement, the varus deformity appeared again. Since childhood, she had been passing stool 3–4 times/day and showed intermittent defecation difficulties, dysuria, weakness in urination and dripping. Physical and neurological examinations showed a lumbosacral mass approximately 0.5 cm in diameter with hair distribution on the surface. Sphincter ani slacked. The patient showed scoliosis, bipedal varus deformity, ankle joint stiffness, poor motion, a heavier right foot, decreased shallow sensation in both lower limbs, especially the heavier foot, level IV muscle strength in the right lower limb, and level IV + muscle strength in the left lower limb. The patient was diagnosed as showing (1) TCS, (2) lumbosacral spina bifida, (3) diastematosi of the spinal cord, (4) meningocele, and (5) scoliosis. The tether-causing factors were categorized under the filum terminal type, cele type, and diastomyelia type. The surgical treatment included bone ridge excision, terminalis disconnection, and dural repair to achieve cord tether release (Figure 1).

3.2.2 Case 2

The patient was a 4-month-old girl who was admitted to the hospital on December 3, 2017 due to progressive enlargement of the lumbar depression for 4 months after birth. At birth, the child was found to have a sunken waist with a diameter of approximately 5 mm and a depth of approximately 0.2 mm, which gradually expanded to a diameter of about 6 mm with a dotted red rash around it. The patient passed soft stools once every 3–4 days. Physical signs and neurological examination showed a skin depression with a diameter of approximately 6 mm and a depth of approximately 0.2 mm in the waist with a

dotted red rash around it. The anus reflexes disappeared on anus relaxation. Limb movement was not abnormal. The diagnosis at admission was TCS with lipomyelomeningocele and congenital spina bifida. The tether-causing factors were categorized under the filum terminal type (double filament), cele type, lipoma type, and arachnoid type. The lipomyelomeningocele was released and returned spinal cord and nerves into the spinal canal in the operation. The lipoma underwent subtotal excision and decompression, and the final filament was cut and the nerve substrate was closed to ensure complete release of the tetracheal cord (Figure 2).

3.2.3 Case 3

The patient was a 36-year-old female who had been experiencing constipation for 34 years and had undergone bipedal deformity surgery 20 years previously who was admitted to the hospital on March 8, 2017 due to weakness of both lower limbs, progressive aggravation of intermittent urinary incontinence for more than 2 years, and significant aggravation for more than 2 months. The patient had been diagnosed as showing a lumbosacral mass at birth, which was resected at the local hospital. She was constipated from childhood, with bowel movements occurring 6–7 days apart. Twenty years before admission, the patient had undergone several procedures for correction of bipedal varus deformity, and her left foot and left ankle were immobile after surgery. Two years before admission, she developed weakness of both lower extremities and progressive aggravation, along with obvious aggravation of the left lower extremity and urinary incontinence with incomplete dripping. Two months before admission, the weakness of the left lower limb worsened significantly, her walking became unstable,

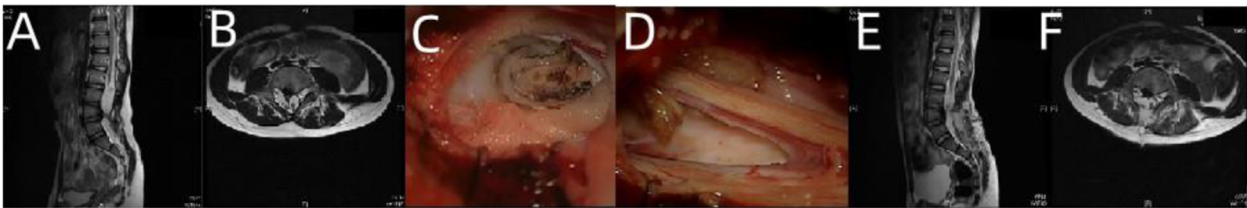


FIGURE 1 Imaging examination and intraoperative findings of case 1 before and after operation. (A,B) Preoperative MRI T2-weighted images of the lumbosacral vertebrae (sagittal and axial) showed diastematosi caused by a bone ridge. (C,D) Image obtained after the bone ridge was exposed and excised during the operation; (E,F) postoperative reexamination showed that the bone ridge was excised and the spinal cord was released satisfactorily.

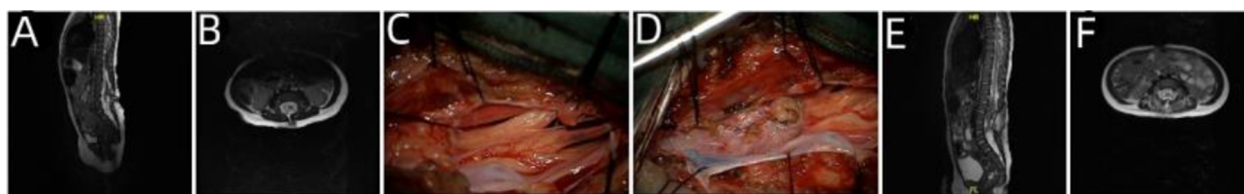


FIGURE 2

Imaging examination and intraoperative findings in case 2 before and after operation. (A,B) Preoperative lumbosacral MRI T2-weighted images (sagittal and axial) showed lipomyelomeningocele. (C) Intraoperative double filaments; (D) the lumen after lipoma resection to avoid postoperative adhesion; (E,F) postoperative reexamination showed that the spinal cord was restored into the spinal canal, the dura was repaired intact, and the spinal cord was released satisfactorily.

her urinary incontinence worsened, and she showed nocturnal enuresis. Physical signs and neurological examination showed surgical scars of approximately 10 cm in length in the lumbosacral region, transverse surgical scars of approximately 6 cm in length in the right heel, and three longitudinal scars of approximately 6 cm in length in the left ankle and left calf. The patient also showed hypoesthesia of the left lower limb, right calf, right foot, and saddle area; bipedal varus deformity, with a more serious deformity in the left foot; grade II muscle strength of the right toe and right ankle and grade IV + muscle strength of the right thigh and right calf; and level 0 muscle strength of the left ankle and left toe and level III + muscle strength of the left thigh and calf muscle. The diagnosis at admission was as follows: (1) TCS; (2) lipomyelomeningocele; (3) spinal lipoma; and (4) congenital spina bifida. The tether-causing factors of the patients were categorized under the cele, lipoma, and arachnoid types. After lipomyelomeningocele release, spinal canal restoration, lipoma subtotal resection, and arachnoid adhesion release were performed to achieve complete release of the tethered cord and spinal canal decompression (Figure 3).

4 Discussion

The characteristics of C-TCS include (1) closely adhered spinal cord and nerve roots that are closely wrapped by arachnoid, lipomatous, and other tissues (11–13); (2) complex lumbosacral vertebral deformities, especially excessive lordosis, kyphosis,

torsion deformation, or severe spinal canal stenosis, which make the anatomical structure more complex and preclude distinction of the normal spinal cord and nerve roots, thus greatly increasing the difficulty of surgery (10, 14); and (3) mixed growth of lipomas and spinal cord lipomyelomeningocele or meningocele and difficulty in decompression of spinal canal contents (8). The imaging findings of patients with C-TCS are more varied and complex than those of patients with common tethered cord syndrome, and the factors causing the tethered cord are complex and sometimes even difficult to identify in C-TCS, necessitating a different choice of surgical options (7, 15). Individualized surgery is more important in the treatment of patients with C-TCS (16–19).

The main objectives of tethered cord release are release and decompression (20, 21) to reduce the spinal cord tension and thereby reduce the rate of retethering (22, 23). C-TCS is called “complex” because these tether-causing factors increase the difficulty of release and decompression, with the filum terminal, arachnoid, bone, and diastomyelia types showing greater difficulty of release and the lipoma and cele types showing greater difficulty of decompression (24–26). Since complete release and full decompression are the primary objectives of tethered cord release (27), an understanding of the tether-causing factors responsible for C-TCS is essential (28, 29). The main factor causing a tethered cord of the filum filament type is the filament, while the secondary factors include lipomas and lipomyelomeningocele/meningocele (30, 31). The arachnoid type is primarily caused by arachnoid adhesion, while the

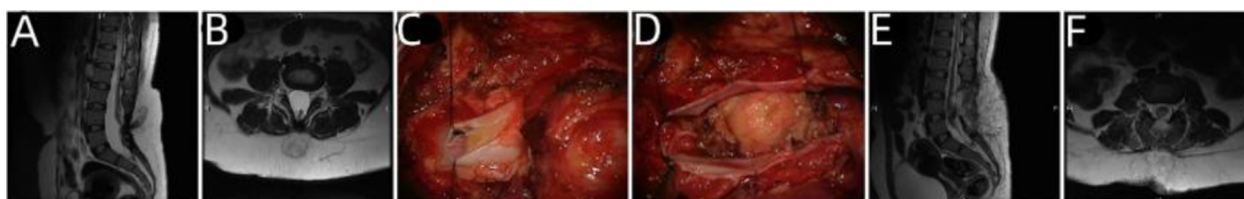


FIGURE 3

Imaging examination and intraoperative findings before and after the operation in case 3. (A,B) Preoperative lumbosacral MRI T2-weighted images (sagittal and axial) showed lipomyelomeningocele. (C) Intraoperative evidence of tissue swelling and lipoma penetrating inside and outside the dura. (D) The spinal cord returned to the spinal canal after lipoma resection. (E,F) Postoperative reexamination showed that the spinal cord was restored into the spinal canal, the dura was repaired intact, and the spinal cord was released satisfactorily.

secondary factors include lipoma and lipomyelomeningocele/meningocele (32, 33). The factors responsible for the cele type include lipomyelomeningocele/meningocele, and the secondary factors include lipoma, spina bifida, and arachnoid adhesion. The primary factor responsible for the lipoma type is lipoma, and the secondary factors include lipomyelomeningocele/meningocele and arachnoid adhesion (34, 35). The primary factor responsible for the bone type is spinal malformation, while secondary factors include thickening of filaments, arachnoid adhesion, and lipomyelomeningocele/meningocele. The primary factor responsible for the diastematosi type is diastematosi of the spinal cord (type I and II), and the secondary factors include spina bifida and arachnoid adhesion (36, 37). Thus, C-TCS is not characterized by the so-called isolated thrombolytic factors and is mediated by the joint action of multiple tether-causing factors. For this reason, accurate differentiation of the responsible tether-causing factors is of great guiding significance for surgery. However, complete release of the tethered cord can only be achieved if all tether-causing factors are addressed, regardless of whether they are primary causative factors or secondary factors (38, 39).

The severity of deformity in TCS has been shown to be directly related to the risk of surgery, and quantifying the complexity of TCS has been a topic of great interest and a difficult problem (40). The causes showing spinal low position, poor spinal motion and spinal cord compression have been analyzed, classified, and summarized into six general tether-causing factors. Using this approach, the complexity of the patient's condition can be preliminarily assessed by analyzing the number of tether-causing factors in each patient (41, 42). In this study, data analysis of 126 patients with C-TCS showed that the more tether-causing factors, the more complicated the condition of patients, the more difficult the operation, the greater the risk of surgery, and the higher the incidence of postoperative complications. In addition, patients with the same number of tether-causing factors also show large differences in performance, so individualized treatment is an important topic that requires further research (43).

The surgical strategies differed according to the factors shown by the patient: (1) the filum filament type required complete disconnection of the filum filament tissue (especially the inner filum filament, since simply disconnecting the outer filum filament cannot achieve the purpose of teaming release), pay more attention to the complete disconnection of the double filum filament to avoid omissions (44). (2) The arachnoid type required detachment of the arachnoid adhesion, which involved first distinguishing the spinal cord, nerves, and hyperplasia of the arachnoid and simultaneous detachment and release of the end of the spinal cord and nerve adhesion to avoid damage to the spinal cord and nerves (45). It was better to distinguish the security interface. (3) In the lipoma type, the spinal cord lipoma usually wraps the end spinal cord, and to avoid damage to the spinal cord and nerves wrapped in the lipoma during the resection process, the lipoma can be removed as much as possible to achieve sufficient decompression while maintaining safety; a

small amount of lipoma can be retained when necessary, but the lipoma must be thoroughly stripped of the adhesion to the surrounding tissue, and the exposed nerve substrate must be sutured to closure. By enlarging the space, reducing the volume of lipoma and closing the wound, the retethering rate was reduced (46, 47). (4) For the bone type, to ensure the stability of the spine, the deformed bone caused by compression should be removed or ground as far as possible, with the purpose of relieving nerve compression, expanding free nerve activity range, reducing retethering rate, and the first or second stages of spinal internal fixation surgery should be performed if necessary (36). (5) In the diastematosi type, the factors causing diastematosi mainly include malformed bone, fibrocartilage, or fibrous frenulum. The diastematosi is usually located above the tethered cord, which should be accurately positioned to avoid excessively long surgical incision. Although the spinal cord showing diastematosi cannot be recovered, the release of spinal cord compression can reduce the tension of the spinal cord and relieve symptoms, at the same time, the integrity of the dura was restored (48). (6) In the cele type, which is often accompanied by spina bifida, most cases show backward bulging, while a few show forward bulging. The bulging spinal cord is completely separated from the adherent subcutaneous tissue and muscle; the spinal cord and nerves are returned to the spinal canal; and the dura is closely repaired, enlarged and repaired if necessary. Advancements in material technology have resulted in ongoing optimization of the biological stability, biosafety and biocompatibility of spinal replacement materials. Thus, an increasing number of patients are choosing to undergo spina bifida repair, restore the integrity of the spinal canal, maintain the stability of the pressure in the spinal canal, and increase the stability of the spine (49).

C-TCS is usually caused by three or more tether-causing factors. Individualized therapy employing different surgical strategies for different patients is important to finally achieve the purpose of complete release of tethered cord (50, 51). For example, in the filum filament + diastematosi type, the location of filament release is located at S1–2, or even lower, and the diastematosi is located at L1–2, which requires two surgical incisions to address both of these factors and achieve the surgical objective. For patients with C-TCS, individualized surgical treatment is aimed at completely releasing the tether while protecting the terminal spinal cord and nerves as much as possible, thereby preventing or delaying the aggravation of neurological dysfunction (52). The number of patients included in this study was slightly insufficient for an in-depth assessment of C-TCS, and data from more cases are needed. Moreover, patients show varying degrees of neurodevelopmental malformation, and in addition to continuing to study the quantitative criteria for TCS severity, the possibility of quantifying individualized treatment is also a topic for further research (53). In addition, the role of each tether-causing factor in spinal cord and nerve injury also needs to be further studied.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the First Medical Center of the PLA General Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

HL: Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft. HS: Data curation, Methodology, Visualization, Writing – original draft. CL: Data curation, Investigation, Validation, Writing – original draft. PZ: Formal Analysis, Software, Writing – review & editing. BX: Conceptualization, Writing – review & editing. YB: Funding acquisition, Project administration, Resources, Writing – review & editing. RX: Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

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Accurate diagnosis and treatment of sacral meningeal cysts without spinal nerve root fibres: identifying leakage orificium using high-resolution spherical arbitrary-dimensional reconstructing magnetic resonance imaging

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Objective: This study aimed to develop an arbitrary-dimensional nerve root reconstruction magnetic resonance imaging (ANRR-MRI) technique for identifying the leakage orificium of sacral meningeal cysts (SMCs) without spinal nerve root fibres (SNRFs).

Methods: This prospective study enrolled 40 consecutive patients with SMCs without SNRFs between March 2021 and March 2022. Magnetic resonance neural reconstruction sequences were performed for preoperative evaluation. The cyst and the cyst-dura intersection planes were initially identified based on the original thin-slice axial T2-weighted images. Sagittal and coronal images were then reconstructed by setting each intersecting plane as the centre. Then, three-dimensional reconstruction was performed, focusing on the suspected leakage point of the cyst. Based on the identified leakage location and size of the SMC, individual surgical plans were formulated.

Results: This cohort included 30 females and 10 males, with an average age of 42.6 ± 12.2 years (range, 17–66 years). The leakage orificium was located at the rostral pole of the cyst in 23 patients, at the body region of the cyst in 12 patients, and at the caudal pole in 5 patients. The maximum diameter of the cysts ranged from 2 cm to 11 cm (average, 5.2 ± 1.9 cm). The leakage orificium was clearly identified in all patients and was ligated microscopically through a 4 cm minimally invasive incision. Postoperative imaging showed that the cysts had disappeared.

Conclusion: ANRR-MRI is an accurate and efficient approach for identifying leakage orificium, facilitating the precise diagnosis and surgical treatment of SMCs without SNRFs.

KEYWORDS

sacral cyst, spinal nerve root, magnetic resonance imaging, sectional reconstruction, leakage orificium

Introduction

Sacral meningeal cysts (SMCs) are cerebrospinal fluid (CSF)-filled extradural meningeal cysts that are most frequently found within the sacral canal and have a prevalence of 4.6%–13.8% in the adult population (1). SMCs are usually asymptomatic, and conditions are usually encountered during radiological screening for sensory discomfort, such as lumbosacral and lower extremity pain and numbness, in neurosurgical, orthopaedic, pain medicine, sports medicine, neurological, and other outpatient clinics (2–4). Patients are also commonly diagnosed when they are examined for anal abnormal sensations, perineal discomfort, or sexual dysfunctions in urology or gynaecology departments (5–7).

In approximately 10%–20% of patients, SMCs may cause symptoms, including local pain, numbness, soreness, and swelling in the lumbar, hip, leg, and perineal areas after prolonged walking or standing, remarkably impairing an individual's quality of life (8–10). In severe cases, patients may experience sexual dysfunction, urinary frequency, constipation, and even urinary and faecal incontinence (2, 3). Therefore, timely and effective surgical treatment is necessary to avoid irreversible nerve damage (7).

Clinically, SMCs can be classified into two types: one type contains spinal nerve root fibres (SNRFs) within the cyst, and the other type lacks SNRFs (2). Surgical strategies vary considerably for these two variants (7). For SMCs with SNRFs, reconstruction of nerve root sleeves can prevent disease progression (2), while for SMCs without SNRFs, the surgical goal should be cyst neck ligation. Notably, SMCs without SNRFs can be further divided into several subtypes according to the pathogenic mechanism involved, including arachnoid hernia, fistula, and filum terminal leakage (2). Currently, identification of the leakage orificium is challenging, which poses great difficulties for surgeons in designing the incision and surgical extent (3). For accurate diagnosis and treatment via minimally invasive procedures, preoperative assessment of the location, size, and leakage orificium of the cysts is necessary (11).

In this study, we used specific thin-slice magnetic resonance images with high resolution and minimum layer thickness; additionally, arbitrary-dimensional reconstruction and layer spacing technology were applied to obtain the optimum images. Using arbitrary-dimensional nerve root reconstruction magnetic resonance imaging (ANRR-MRI), we identified the leakage orificium of SMCs without SNRFs, and its value for accurate diagnosis and treatment was demonstrated.

Materials and methods

Patients

This prospective study enrolled 40 consecutive patients who were diagnosed with SMCs without SNRFs between March 2021 and March

2022. All these patients had symptoms and signs, providing a definitive indication for surgical treatment. All SMCs containing any identifiable SNRFs within the cyst on neuroimaging were excluded. This prospective study was approved by the Institutional Review Board and Ethics Committee of Peking University Third Hospital (M2021048).

Radiological processing

Neuro-microstructure reconstruction was performed based on MR 3D fast imaging employing the steady-state acquisition (3D-FIESTA) technique, an improved version of the 3D FIESTA sequence, using a Discovery MR750 3.0T MR system (GE Healthcare, Milwaukee, WI, United States) with a spinal coil. The scans included conventional T1-weighted, T2-weighted, and three-dimensional T2-weighted (3D-T2WI) axial nerve root reconstruction sequences. The 3D-T2W axial original images were then transferred into a GE AW4.6 reformat and 3D-MIP workstation.

High-resolution arbitrary-dimensional spherical curve planar reformation was performed. Based on the 3D-T2W axial thin-slice images, the cyst and the cyst-dura intersection planes were initially identified. Sagittal and coronal images were then reconstructed by setting each intersecting plane as the centre. Then, three-dimensional reconstruction was performed, focusing on the suspected leakage orificium of the cyst. The reconstructed images were subsequently imported into the PACS imaging system, after which the location and size of the SMCs were assessed.

Surgical plan and intraoperative monitoring

On the high-resolution 3D-FIESTA-C images, the cyst and SNRFs were clearly displayed in two-dimensional form. Based on the reconstructed images, a surgical plan was designed that included the exact location of the cyst leakage orificium, the skin incision, and the bone window.

The locations of the cyst leakage orificium were classified into upper, middle, and lower segments, and the precise incision was made by setting the leakage orificium as the centre. Leakage was further classified into four types: arachnoid hernia, fistula, filum terminal leakage, and spinal dura mater leakage. Additionally, the maximum diameter of the cyst was measured as a preliminary preparation for designing a precise surgical incision and formulating a surgical plan.

Intraoperatively, electrophysiological monitoring was used to guarantee neural integrity, especially when the nerve structures were dissected from the cyst wall. Under the microscope, the cyst was opened to determine whether the nerve structures penetrated through or adhered to the wall internally. For larger cysts, after the leakage was

sutured or ligated, the upper- or lower-pole distal cyst residue was left untreated.

Postoperative follow-up

Postoperatively, patients were followed up at specific intervals (1 week postoperatively, 3 months postoperatively, 6 months postoperatively, and 1 year thereafter) to monitor the recovery of neurological dysfunctions, residual symptoms, and radiological absorption of the untreated portion of the cyst.

Results

Clinical and radiological characteristics

This cohort included 30 (75.0%) females and 10 (25.0%) males. The age of the patients ranged from 17 to 66 years, with a mean of 42.6 ± 12.17 years. The leakage orificium was located at the rostral pole of the cyst in 23 (57.5%) patients, at the body region of the cyst in 12 (30.0%) patients, and at the caudal pole (12.5%) in 5 patients. The maximum diameter of the cysts ranged from 2 cm to 11 cm, with a mean of 5.2 ± 1.9 cm.

With the use of nerve root magnetic resonance reconstruction technology, the cystic leakage orificium was accurately identified in all patients preoperatively, with an accuracy of 100%. Based on the magnetic resonance images, a precise minimally invasive incision was designed with a length of 4–5 cm, and intraoperatively, the skin incision was made based on the bone landmarks, including the crista iliaca and the coccygeal tip. The duration of the operation ranged from 1.5 to 2.5 h, with a blood loss of only 10–30 mL (Figure 1).

Among these patients, 38 had an isolated cyst, two had multiple cysts, and two had concomitant sacroanterior cysts. Based on the leakage morphology, 15 (37.5%) patients had filum terminale cysts, 14 (35.0%) had an arachnoid hernia, 6 (15.0%) had spinal dura mater leakage, and 5 (12.5%) had fistulas. Among all the cysts, 34 (83.0%) were located in the midline, 4 (9.7%) were on the left side, and 3 (7.3%) were on the middle line.

Neurological assessments

All 40 patients (100.0%) presented with chronic lumbosacral or perineal pain, and 22 (55.0%) patients presented with numbness in the perianal region and lower extremities. Preoperatively, 15 patients had no bowel or bladder dysfunction, and none of them experienced any functional deterioration after surgery. There were varying degrees of bowel and/or bladder dysfunction in 25 patients, among whom 15 (37.5%) had mild dysfunction, such as urinary frequency and constipation; 7 (17.5%) had moderate dysfunction, including difficulty urinating and defecating; and 3 (7.5%) had incontinence. These patients were discharged after removal of the urethral catheter on postoperative days 7–10, and routine nutritional and neural rehabilitation therapy was continued. During the follow-up period, 15 patients achieved completely normal bowel and bladder functions, and 10 patients experienced varying degrees of improvement (Figures 2–4).

Surgical treatment

Four patients had received fat or muscle grafting and biological glue fixation at local hospitals, among whom one patient also underwent lumbar-sacral vertebral reinforcement internal fixation. However, postoperative recurrence of the cyst was noted, and the patient was referred to our institute. After comprehensively evaluating the cysts and involved nerve roots via reconstructed magnetic resonance imaging, precise minimally invasive surgery was performed. The leakage orificium was accurately identified and ligated. Postoperatively, the cysts had disappeared, and the symptoms were relieved (Figure 5). During the follow-up, no cyst recurrence was demonstrated.

Representative complicated cases

Two female patients with sacroanterior cysts were misdiagnosed with pelvic masses during their first surgeries, both of whom underwent laparoscopic exploration at local hospitals. The first is a 22-years-old woman who presented with sacrococcygeal pain and

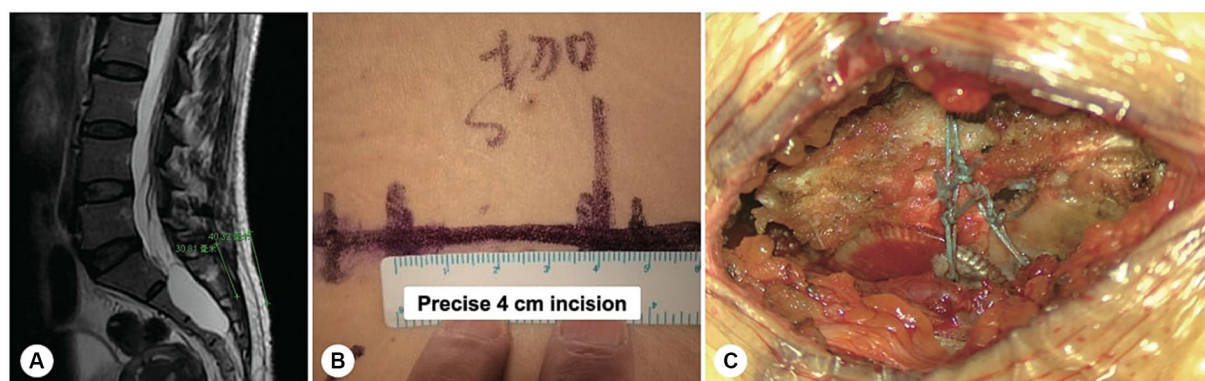


FIGURE 1

A precise incision was made for a sacral meningeal cyst without spinal nerve root fibres. (A) Spinal T2-weighted MR image demonstrating a sacral meningeal cyst without spinal nerve root fibres inside, and a precise incision was made as indicated by the green line. (B) The precise incision on the skin was only 4 cm in length. (C) After the cyst neck was ligated, the posterior wall of the sacral canal was reset using bone fixators.

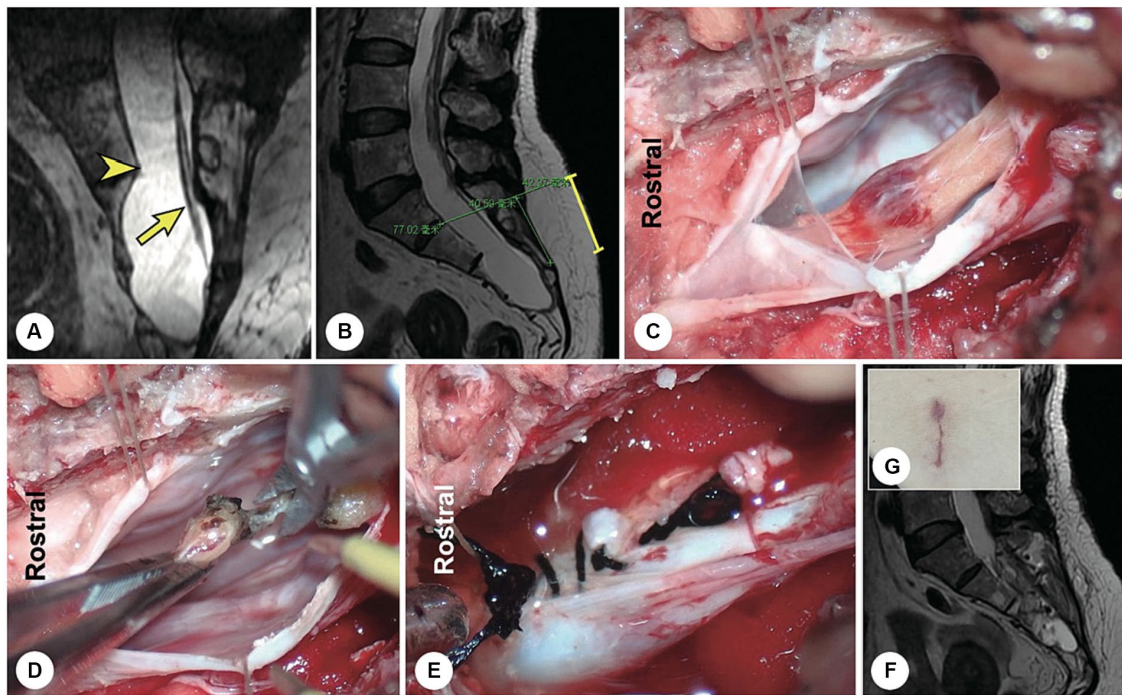


FIGURE 2

A representative patient with a filum terminale cyst. (A) Preoperatively, reconstructed spinal MR image showing a sacral cyst at the S2-4 level with a thickened filum terminale and wide leakage neck (the arrowhead indicates the cystic leakage orificium, and the arrow indicates the filum terminale). (B) A 4 cm precise minimally invasive incision was made (yellow line segment). (C) Intraoperatively, the filum terminale was found within the cyst cavity. (D) The filum terminale was cut off after electric coagulation. (E) The leakage orificium was ligated. (F) Follow-up MRI showed that the cyst had disappeared and that there was no recurrence. (G) The 4 cm long skin incision healed well.

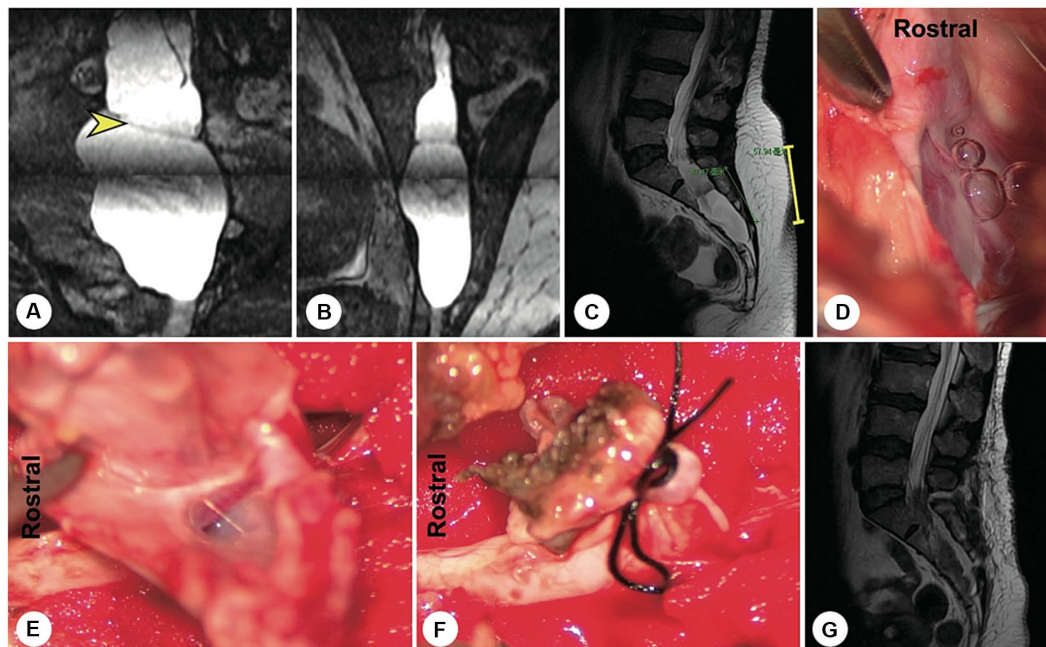


FIGURE 3

A representative patient with a fistula-type cyst. (A,B) Preoperatively, reconstructed MR image showing a fistula between the dural sac and the cyst (yellow arrowhead). (C) A 5 cm precise minimally invasive incision was designed (yellow line segment). (D) Intraoperatively, a fistula-type cyst was found, and there was no nerve root. (E) The cyst wall was dissected and turned over. (F) The cyst neck was ligated. (G) Follow-up MRI showed that the cyst had disappeared and that there was no recurrence.

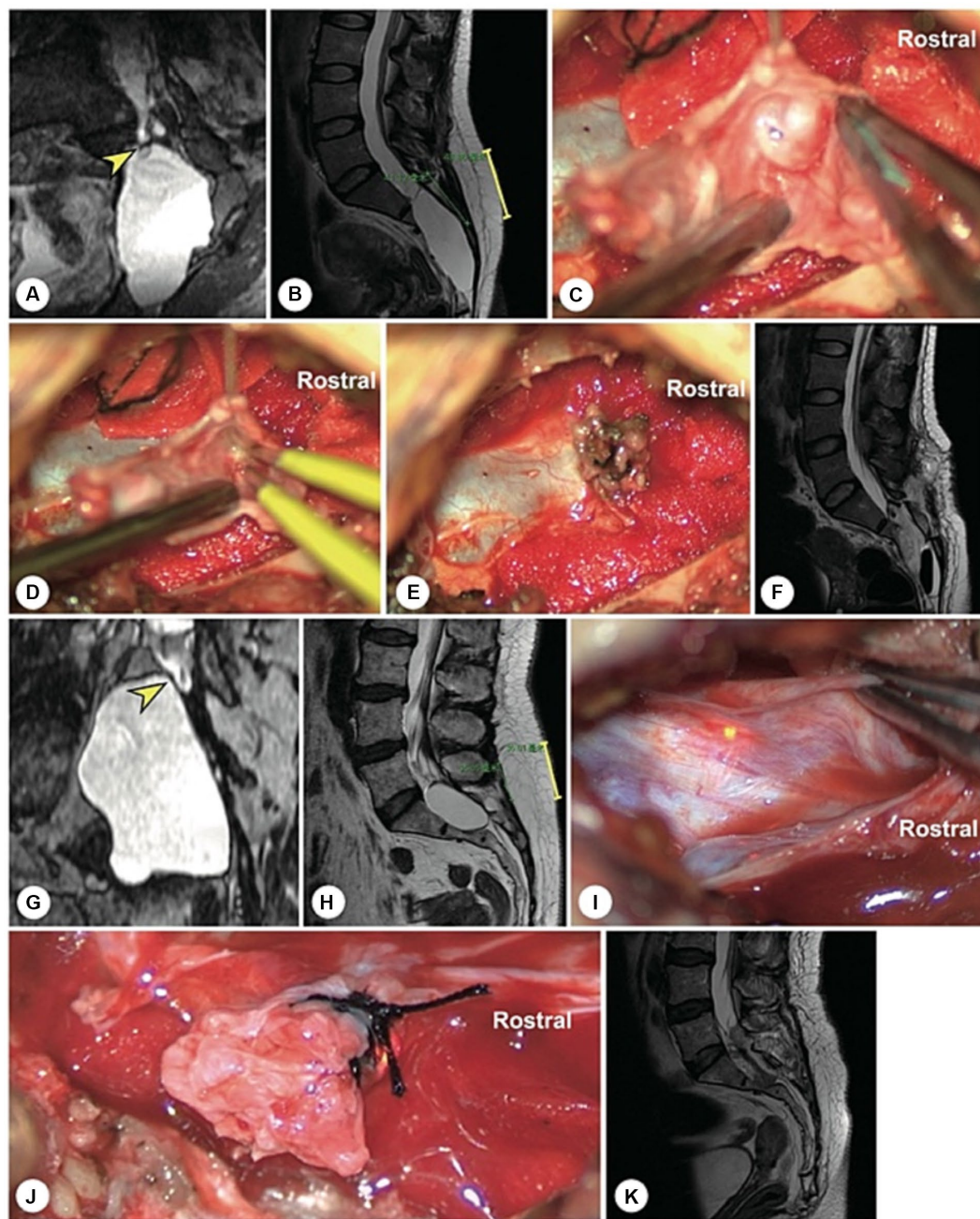


FIGURE 4

A representative case of an arachnoid hernia-type cyst and a representative case of a spinal dura mater leakage cyst. (A) Preoperatively, reconstructed MR image revealing an arachnoid structure within the cyst (the yellow arrowhead indicates the cystic leakage orificium). (B) A 4 cm precise and minimally invasive incision was made (yellow line segment). (C–E) Intraoperatively, an arachnoid diverticulum was found as the origin of the cerebrospinal fluid, and this cystic leakage orificium was ligated. (F) Follow-up MRI showed that the cyst had disappeared and that there was no recurrence. (G) Preoperatively, reconstruction MRI showed that the narrow end of the dural sac was squeezed to the left by a giant cyst without nerve roots (the yellow arrowhead indicates the cystic leakage orificium). (H) A 4 cm precise minimally invasive incision was made (yellow line segment). (I) Intraoperatively, we found that the lateral wall of the dural sac was weak, leading to leakage. (J) The cyst wall was dissected and turned over. (K) Follow-up MRI showed that the cyst had disappeared and that there was no recurrence.

sphincter disturbances. MRI revealed a large sacroanterior cyst originating from the sacral canal (Figure 6). After referral to our hospital, high-resolution spherical arbitrary-dimensional reconstructed MRI demonstrated that the cyst leakage orificium originated from the end of the dura mater and that there were no SNRFs within the cyst. With a precisely designed skin incision and

bone window, the leakage orificium was ligated. Six months after surgery, the sacroanterior and sacral cysts had disappeared completely.

The other patient was a 45 years-old female whose sacroanterior cyst in the pelvic cavity had been partially resected during the first exploratory surgery. Intraoperatively, the local surgeon attempted to clip the leakage orificium of the cyst with a titanium clip.

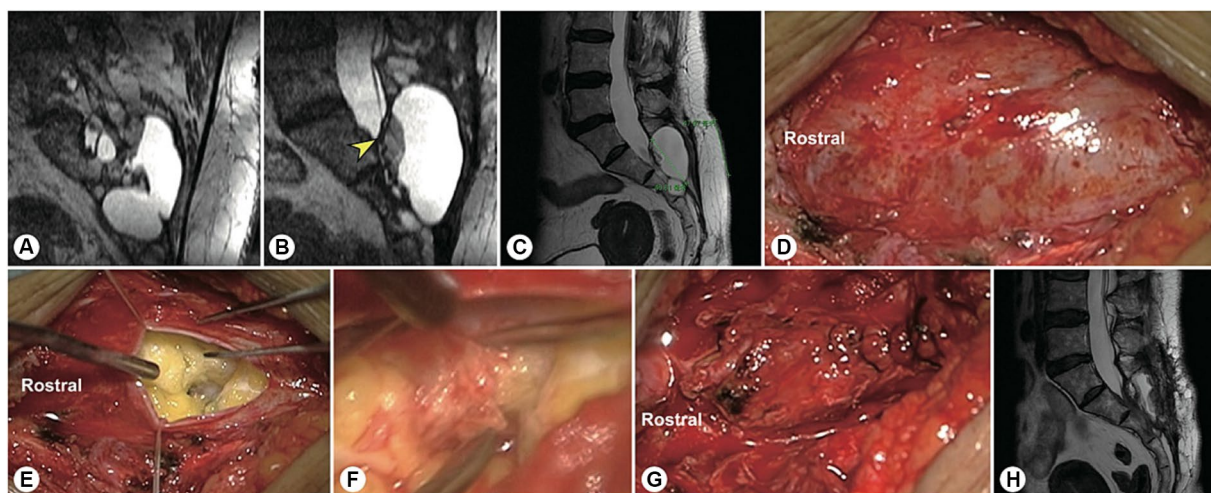


FIGURE 5

A representative patient with a massive sacral meningeal cyst. A 56 years-old woman with a massive sacral cyst was treated with glue injection and fat filling at the local hospital. (A) After referral to our institute, reconstructed MR image showed a sacral meningeal cyst and an extrasacral cyst, which were separated by the filled fat mass. (B) Sagittal spinal T2-weighted MR image showing the distorted dura sac end, dorsal fat mass, and residual cyst. (C) The precision of the incision is indicated by the green line. (D) Intraoperatively, a pseudocyst was found under the muscle layer. (E) After the pseudocyst was opened, cerebrospinal fluid was found to leak from the centre of the tightly packed fat. (F) After the filled fat was separated, the hardened biological glue was exposed. (G) After the neck of the cyst leakage site was sutured, the end of the dural sac was reinforced by an artificial dural membrane. (H) Two months after surgery, repeated MRI showed no cyst recurrence.

Unfortunately, postoperative cerebrospinal fluid leakage occurred, and she was then transferred to our hospital. High-resolution spherical arbitrary-dimensional reconstructed MR images confirmed that the sacroanterior and sacral cysts originated from the end of the dura mater and contained no SNRFs. With a precise surgical incision along the midline of the sacrum, the cyst neck was accurately ligated. The patient recovered completely during the follow-up (Figure 7).

Discussion

SMCs refer to diverticula of the arachnoid mater, dura mater, or nerve root sheath that may occur in the perineural, extradural, or intradural regions, respectively. These entities are relatively rare, accounting for approximately 1% of all spinal lesions (12). Previously, SMCs were also referred to as arachnoid cysts or meningeal diverticula. The majority of SMCs are asymptomatic and are detected incidentally via MRI. Michael Nabors classified spinal cysts into three categories: (a) meningeal cysts, (b) nonmeningeal epidural cysts, and (c) neurenteric cysts. Spinal meningeal cysts are further divided into three subtypes: (a) type I, extradural meningeal cysts containing no SNRFs, including extradural arachnoid cysts (type Ia) and sacral meningoceles (type Ib); (b) type II, extradural meningeal cysts containing SNRFs; and (c) type III, intradural meningeal cysts (13). In 2013, we summarized our previous clinical experience in the treatment of type I and type II SMCs (2, 3). In 2016, we proposed a distinct subtype of smooth muscle cells (SMCs), filum terminale cysts without SNRFs, which are usually accompanied by spinal cord tethering (4). For these patients, the surgical strategy should not be limited to suturing or ligating the cyst neck but should include releasing the tethered spinal cord.

The surgical goal for treating SMCs without SNRFs is to restore the normal anatomical structure of the terminal cisterna and the nerve root sleeve and to suture or ligate the neck or fistula of the cyst (14).

Previously, several scholars have used procedures such as puncture, suction, and injection of glue to treat smooth muscle cells (SMCs) (9, 15, 16). These methods cannot reconstruct the anatomical structure of the nerve root sleeve, and blind puncture may stimulate or even injure the nerve root. In particular, these procedures are associated with a high recurrence rate, which seriously affects patients' quality of life (8, 17, 18). In our cohort, four patients underwent reoperation after repeated aspiration, multiple injections of glue, or filling with fat and muscle in local hospitals. Additionally, filled biological glue and fat may cause space-occupying effects, compressing normal nerve structures and affecting the function of SNRFs (19). Moreover, these procedures may lead to local adhesions, inevitably aggravating symptoms after the operation (20).

Intraoperative suturing or ligation of the neck or fistula of the cyst is essential for SMCs without SNRFs. To prevent further impairment of the cyst wall by the SNRFs, the remaining cyst was left. The precise incision design is predicated on the accurate location of the cyst leakage orificium with the assistance of reconstructed MRI (21). In the present study, we divided the SMCs without SNRFs into four types: filum terminale cysts, accounting for 37.5%; arachnoid hernias, accounting for 35.0%; spinal dura mater leakage, accounting for 15.0%; and simple fistulas, accounting for 12.5%. The optimal surgical approach for various subtypes of patients should be distinct and individualized and should be adjusted appropriately. For filum terminale cysts, the internal or external filum terminale should be cut, while the cyst neck should be sutured or ligated, after which the filum terminale is released. For arachnoid hernia cysts, electrocautery and ligature were performed sequentially to reinforce the arachnoid membrane. For simple fistulas, direct suturing and ligatures were sufficient. For spinal dura mater leakage, after suturing and ligature, the dural sac end was reinforced (1, 22).

Some SMCs may be accompanied by sacroanterior cysts. The sacral and sacroanterior portions are usually connected, and the

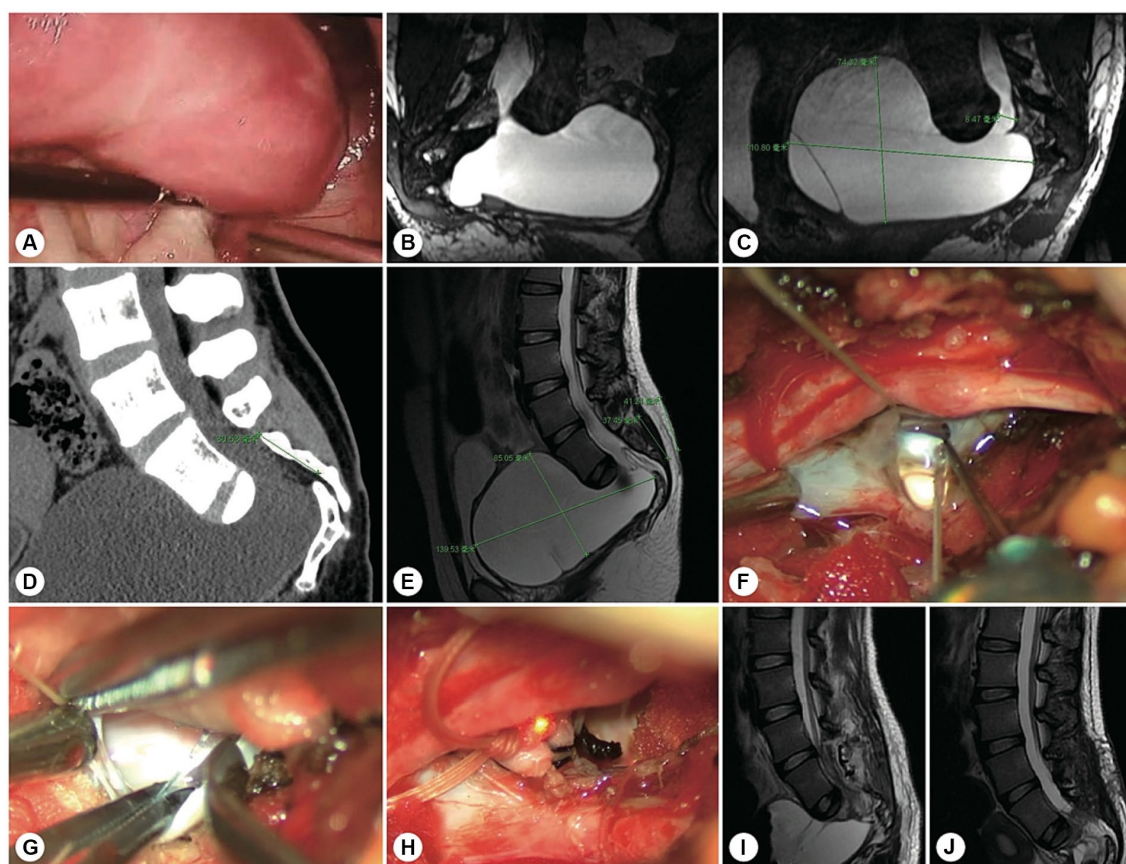


FIGURE 6

A representative patient with both sacroanterior and sacral cysts. A 22 years-old woman presenting with abdominal pain was found to have a pelvic mass. (A) Laparoscopic exploration revealed that the pelvic lesion was connected to the sacral canal. (B) Coronal MR image showing wide neck leakage between the end of the dural sac and the sacral canal. (C) Sagittal MR image revealing a giant sacroanterior cyst connected to a sacral cyst without nerve root fibres inside. (D) Sagittal CT image showing a sacroanterior bone defect. (E) A precise incision was made. (F) Intraoperatively, abundant cerebrospinal fluid leaked from the orificium, suggesting high intracystic pressure. (G) No spinal nerve root fibres were identified in the leakage orificium. (H) The leakage orificium was ligated. (I) On MRI, 1 week after the operation, the sacroanterior cyst had shrunk. (J) Three months after surgery, the sacroanterior cyst had almost completely disappeared on MRI.

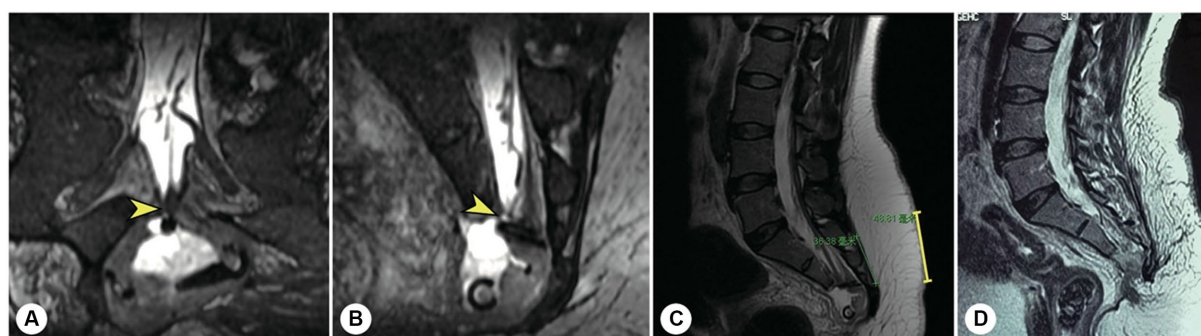


FIGURE 7

The other representative patient had both sacroanterior and sacral cysts. A 45 years-old female presenting with abdominal pain was found to have a pelvic mass on CT at the local hospital. The intrapelvic part of the cyst was resected under laparoscopy. (A) After referral to our institute, coronal reconstructed MR image showed a narrow-neck leakage orificium (yellow arrowhead) between the end of the dural sac and the sacral canal cyst, and the filum terminale was thickened. (B) Sagittal reconstructed MR image showing the leakage orificium (yellow arrowhead) at the end of the dural sac connected to the sacral cyst and the residual sac. (C) A 4 cm precise incision was made (yellow line segment). (D) After the leakage orificium was ligated and the tethered spinal cord was released, a follow-up MRI showed that the cyst had completely vanished.

joint between the sacral canal and the dura mater is often the origin of the leakage orificium. As the intrasacral portion of the cyst gradually increases in size and breaks through the boundary of the sacroanterior bone, the sacroanterior region also becomes involved. Clinically, sacroanterior cysts often manifest as abdominal pain. Preoperative sacrococcygeal MRI is strongly recommended for diagnosis. For these patients, laparoscopic exploration and removal of the pelvic mass are highly risky and may cause irreversible and life-threatening continuous cerebrospinal fluid leakage and neurological infections (23). In our experience, complicated sacroanterior-sacral cysts without SNRFs can be effectively treated by suturing or ligating the leakage via a posterior approach. The cyst may disappear gradually after the operation. In the future, with the development of molecular biology techniques, additional disease-related biomarkers will be discovered, and nonsurgical treatment strategies may be developed (24, 25). However, currently, surgical treatment is the exclusive approach for relieving symptoms in a considerable proportion of patients (26, 27).

3D-FIESTA imaging is highly valuable for identifying nerve roots and leakage orificia (28). This sequence can compensate for the deficiencies of T1-FLAIR and T2WI, and the nerve roots often exhibit clear hypointensity, resulting in a sharp contrast with the hyperintensity of the cystic fluid. Moreover, this sequence is a 3D scan that can be reconstructed in any spherical dimension and displays the three-dimensional anatomical relationship between nerve roots and cysts from different angles. Additionally, high-resolution curve planar reformation can reveal the complete nerve pathway that enters the sacral cyst in a curved manner, as well as the possible presence of leakage (28).

Based on 3D thin-slice axial T2-weighted imaging, repeated spherical reconstruction in arbitrary dimensions can determine the number and trajectory of neural roots within the cyst as well as the location of the leakage orificium. The surgical incision and bone window were designed by setting the leakage orificium as the centre, and the length of the incision was adjusted according to the thickness of the soft tissue outside the posterior wall of the sacral canal. Then, with the use of an ultrasonic bone knife, the bone window was precisely opened, and after the cyst was processed, the posterior wall of the sacral canal was perfectly reset and fixed.

Conclusion

Our study demonstrated the potential of using ANRR-MRI for accurate diagnosis and treatment of SMCs without SNRFs. With the use of this technique, we were able to accurately predict the location and size of the leakage orificium preoperatively and formulate precise surgical plans. However, additional studies with larger sample sizes are needed to confirm the effectiveness of this approach and to explore its potential in other fields of neurosurgery.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Institutional Review Board and Ethics Committee of Peking University Third Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CY: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing – original draft, Writing – review & editing. XL: Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. LH: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. QM: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. XY: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. QZ: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. CW: Data curation, Formal analysis, Investigation, Writing – review & editing. HW: Writing – review & editing. JS: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer HT declared a shared affiliation with the author JS to the handling editor at the time of review.

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Effects of peak ankle dorsiflexion angle on lower extremity biomechanics and pelvic motion during walking and jogging

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Objective: Ankle dorsiflexion during walking causes the tibia to roll forward relative to the foot to achieve body forward. Individuals with ankle dorsiflexion restriction may present altered movement patterns and cause a series of dysfunction. Therefore, the aim of this research was to clearly determine the effects of peak ankle dorsiflexion angle on lower extremity biomechanics and pelvic motion during walking and jogging.

Method: This study involved 51 subjects tested for both walking and jogging. The motion capture system and force measuring platforms were used to synchronously collect kinematics and kinetics parameters during these activities. Based on the peak ankle dorsiflexion angle during walking, the 51 subjects were divided into a restricted group (RADF group, angle <10°) and an ankle dorsiflexion-unrestricted group (un-RADF group, angle >10°). Independent-Sample *T*-tests were performed to compare the pelvic and lower limb biomechanics parameters between the groups during walking and jogging test on this cross-sectional study.

Results: The parameters that were significantly smaller in the RADF group than in the un-RADF group at the moment of peak ankle dorsiflexion in the walking test were: ankle plantar flexion moment ($p < 0.05$), hip extension angle ($p < 0.05$), internal ground reaction force ($p < 0.05$), anterior ground reaction force ($p < 0.01$), pelvic ipsilateral tilt angle ($p < 0.05$). In contrast, the external knee rotation angle was significantly greater in the RADF group than in the un-RADF group ($p < 0.05$). The parameters that were significantly smaller in the RADF group than in the un-RADF group at the moment of peak ankle dorsiflexion in the jogging test were: peak ankle dorsiflexion angle ($p < 0.01$); the anterior ground reaction force ($p < 0.01$), the angle of pelvic ipsilateral rotation ($p < 0.05$).

Conclusion: This study shows that individuals with limited ankle dorsiflexion experience varying degrees of altered kinematics and dynamics in the pelvis, hip, knee, and foot during walking and jogging. Limited ankle dorsiflexion alters the movement pattern of the lower extremity during walking and jogging, diminishing the body's ability to propel forward, which may lead to higher injury risks.

KEYWORDS

ankle dorsiflexion, kinematics, kinetic, gait, jogging

1. Introduction

The range of motion of ankle dorsiflexion was defined as the talus rolls forward relative to the leg and at the same time slides posteriorly (talocrural dorsiflexion) (1). Adequate ankle dorsiflexion range of motion is necessary for daily functional activities such as walking, jogging, landing, and walking up and down stairs (2). During the stance phase of gait, dorsiflexion reaches the peak just before heel rise. It was shown that the magnitude of ankle dorsiflexion varies among individuals, it is generally in the range of 5–15 degrees, with a minimum of 10 degrees reported by Root et al. (3). Ankle dorsiflexion during walking causes the tibia to roll forward relative to the foot to achieve body forward (1, 4). Jogging, on the other hand, requires a greater angle of ankle dorsiflexion to achieve forward rolling (5).

Reduced ankle dorsiflexion is primarily caused by tightness in the gastrocnemius and soleus and insufficient posterior gliding of the talus and is also associated with musculoskeletal injuries of the foot and ankle joint (6). Some researchers have identified ankle dorsiflexion restriction has been indicated as a dangerous factor for lower extremity injuries (7–10) and can lead to compensatory movements that alter lower extremity movement patterns and generate excessive stress. These biomechanical changes can result in injuries such as plantar fasciitis (8, 11), Achilles tendinitis (12), and knee injuries due to altered knee alignment (13, 14). Moreover, limited ankle dorsiflexion leads to changes in pelvic movement patterns (15), and studies have indicated (16) that the lumbar-pelvic movement patterns are altered in patients with low back pain compared to those without low back pain, and that inadequate individual control of gait and abnormal lower limb biomechanics can produce excessive stress on the upper lumbosacral region, leading to the development of low back pain (17–19). Previous studies have shown that a decrease in ankle dorsiflexion angle leads to an increase in foot progression angle during the gait cycle (20), an earlier heel-off time (21), and a shorter stride length (22). From the point of view of the coupling pattern of the kinematic chain, the movement of the ankle may affect the temporal and movement parameters of the knee, hip, and pelvis (23). Inadequate ankle dorsiflexion affects the ability to move forward (24), preferring to land on the arch of the foot and the front foot, affecting ground reaction forces and the torque of the lower extremity joints (25, 26). It also alters peak hip and knee flexion and pelvic movement patterns during the swing phase (15). Therefore, the limitation of ankle dorsiflexion restriction can cause a series of dysfunction, and it is important to clarify the specific effect of ankle dorsiflexion angle on lower extremity biomechanics and pelvic movement for the prevention and treatment of functional impairment.

The influence of limited ankle dorsiflexion on certain lower extremity joint motion biomechanical parameters during walking has been investigated in the literature, but no study has yet investigated the effect of different angular range on overall lower extremity biomechanics as well as pelvic motion during jogging and further compared it with lower extremity biomechanics during walking. Therefore, the aim of this research was to compare the lower limb and pelvic biomechanics during the stance phase of gait between individuals with lower and higher peak ankle dorsiflexion angle and clearly determine the effects of different peak ankle dorsiflexion angle on the kinematics and kinetics of the hip, knee, and ankle joints in different planes of motion during walking and jogging, as well as on pelvic motion. The main hypothesis of this study is that individuals with limited peak ankle dorsiflexion angles have reduced knee and hip

motion in the sagittal plane during walking and jogging tests, altered pelvic motion patterns, and reduced ground reaction forces corresponding to peak moments of ankle dorsiflexion in gait.

2. Materials and methods

2.1. Participants

This study was approved by the Ethics Committee of Peking University Third Hospital. And the study authorization number was M2023360 (June 23, 2023). All participants read and signed an approved informed consent document before data collection. 51 subjects (35 men and 16 women) volunteered for this cross-sectional study. The inclusion criteria were (1) age 18–40, BMI (body mass index) in the normal range (18.5–24.9) (2) no neurological disorders (3) no musculoskeletal disorders within the last 6 months that limited their physical activity (4) no surgery or acute injury history to the lower extremities or pelvis. All of these 51 subjects had sufficient physical strength to perform at least 5 sessions of walking and jogging tests and no complaints of pain or discomfort during data collection. 13 subjects showed limited dorsiflexion in squatting, which is defined as that the knee joint could not fully flexed or the heel would have to raise during squatting with the feet shoulder-width apart. The other 38 people were able to complete the squat test successfully without limited dorsiflexion.

Previous research experiments have used ankle dorsiflexion range of motion measurement techniques mostly in passive flexion of the ankle joint under non-weight-bearing conditions (3, 15, 20) or using a weight-bearing lunge position for measurement (27, 28). In contrast, the present study innovatively selected the peak ankle dorsiflexion angle during the support phase of the walking test as the criterion for differentiating whether subjects had limited ankle dorsiflexion. This method can more accurately confirm whether an individual has an appropriate ankle range of motion during walking or other functional movements.

Fifty-one subjects were divided into groups based on the peak ankle dorsiflexion angle during the support phase of the walking test. Subjects with a peak ankle dorsiflexion angle of less than 10° on either side during the walking test were included in the ankle dorsiflexion-restricted group (ankle dorsiflexion angle less than 10°, $n = 30$, hereinafter referred to as RADF group), while other subjects were included in the ankle dorsiflexion-unrestricted group (ankle dorsiflexion angle greater than 10°, $n = 21$, hereinafter referred to as un-RADF group). The sample size was calculated using G*Power software in this study, with an α level of 0.05 and statistical power of 80%, and an estimated effect size of 1.0. Based on the difference between groups on the main outcome measures peak knee external rotation obtained in a pilot study with ten individuals. A minimum of 20 participants per group was needed to detect between-subject differences. 10 subjects in the pilot study were from the Outpatient Department of Sports Medicine, Peking University Third Hospital. They all received ankle physical examination and questionnaire survey, and 5 subjects were limited in squatting.

2.2. Data collection

The subject's static and dynamic 3D motion information was collected with an 8-camera infrared high-speed motion capture

system (Vicon, T40) at 100 Hz. Kinetic parameters were collected with 2 3D force platforms (AMTI, BP400600) at 1000 Hz. Kinematic and kinetic data were synchronized by a synchronization box (AMTI, GEN5). Subjects were labeled with reflective marker dots on the bony parts and the model was optimized using the international general model plug-in-gait.

Subjects wore exercise shorts to fully expose the waist and mid-thigh below. After the reflective markers were fixed, subjects followed the test procedure to first familiarize themselves with the collection exercise requirements and process. The subjects stood in the center of the chamber with their feet shoulder-width apart and both upper extremities placed naturally on both sides of the body, maintaining a neutral position of the talofibular joint for three static tests to collect static data for defining the coordinate system of the skeletal segments. Subsequently, the subjects were tested by walking and jogging at a self-selected speed. The interval between the two tests was such that the subjects did not feel exerted. 5 valid data were collected for each movement and the average of the 5 tests was used for analysis. The whole tests were carried out in a space of 10 m long, 8 m wide and 3 m high, and the length of test tracking area was about 6 m.

2.3. Data processing

The lower extremity kinematic data from the subjects' walking test and jogging test were processed, and the subjects were divided into the RADF group ($<10^\circ$, $n = 30$; 22 men) and un-RADF group ($>10^\circ$, $n = 21$; 8 men) according to the peak ankle dorsiflexion angle during the support period in the walking test. The biomechanical model of the rigid body was developed using a static test with the talocrural joint in a neutral position. The force platform determines the occurrence of heel-strike and toe-off the ground by using ground reaction forces to determine the stance phase of the entire gait process. The coordinate data were filtered using a low-pass butter-worth filter at 12 Hz. The ground-reaction force data were filtered using a lowpass butter-worth filter at 100 Hz. Time-series data for the kinematics and kinetics variables in the coronal, sagittal, and horizontal planes of the pelvis, hip, knee, and ankle joints were calculated using Visual 3D software (Cmotion, Germantown, MD version v6.00.18).

2.4. Data analysis

All statistical analyses were completed using SPSS 26.0 (IBM, New York, USA). Quantitative data were first tested for normality, and if they conformed to a normal distribution, they were expressed as

mean $\pm$ standard deviation and subjected to a two-sample *t*-test; if they did not conform to a normal distribution, they were expressed as median and quartiles and subjected to a two-sample rank sum test. The significance level was set at a class I error probability of no greater than 0.05.

3. Results

3.1. Participant information

A total of 51 subjects participated in the study, including 25 men and 16 women. The RADF group ($<10^\circ$, $n = 30$; 22 men) and un-RADF group ($>10^\circ$, $n = 21$; 8 men). 17 of the 38 subjects who were not limited in squatting were classified in the RADF group based on the results of the walking test. The 30 subjects in the RADF group included 13 with passive limited dorsiflexion and 17 without passive limited dorsiflexion during squat test. There was no significant difference in age, height, and weight between the RADF group and un-RADF group ($p > 0.05$; see Table 1).

3.2. Walking

Figure 1 shows the variations of joint motion angles in the coronal, sagittal, and horizontal planes of the pelvis and lower extremities during the stance phase of the walking process in the two groups of subjects. Figure 2 shows the variations of moments in the coronal, sagittal, and horizontal planes of each joint of the lower extremity during walking in the two groups of subjects. Table 2 shows the results of comparing the lower limb biomechanical parameters at the moment of peak ankle dorsiflexion angle during the stance phase of gait. The parameters that were significantly smaller in the RADF group than in the un-RADF group were: peak ankle dorsiflexion angle (RADF group: $6.20 \pm 2.59^\circ$, un-RADF group: $13.52 \pm 1.96^\circ$, $p < 0.01$); ankle plantarflexion moment corresponding to this peak moment (RADF group: 0.75 ± 0.15 BW* BH, un-RADF group: 0.84 ± 0.05 BW* BH, $p < 0.05$), hip extension angle (RADF group: $5.73 \pm 6.72^\circ$, un-RADF group: $9.93 \pm 6.21^\circ$, $p < 0.05$), internal ground reaction force (RADF group: 0.05 ± 0.02 BW, un-RADF group: 0.06 ± 0.02 BW, $p < 0.05$), anterior ground reaction force (RADF group: 0.10 ± 0.04 BW, un-RADF group: 0.14 ± 0.02 BW, $p < 0.01$), and pelvic ipsilateral tilt angle (RADF group: $0.82 \pm 1.53^\circ$, un-RADF group: $1.81 \pm 1.66^\circ$, $p < 0.05$). In contrast, the external knee rotation angle was significantly greater in the RADF group than in the un-RADF group (RADF group: $3.34 \pm 2.84^\circ$, un-RADF group: $1.04 \pm 4.46^\circ$, $p < 0.05$). No significant differences were found between other biomechanical parameters of the lower extremities and the pelvis.

TABLE 1 Participant information.

Variables	un-RADF group (SD)	RADF group (SD)	<i>t</i> -value	<i>p</i> -value	Mean difference (95% CI)
Height (cm)	170.95 (5.84)	173.07 (8.43)	−0.99	0.33	2.11 (−2.17 to 6.39)
Body mass (kg)	70.62 (11.81)	72.48 (13.43)	−0.51	0.61	1.86 (−5.46 to 9.17)
Age (years)	26.38 (8.70)	29.83 (10.18)	−1.26	0.21	3.45 (−2.04 to 8.94)

SD, standard deviation; CI, Confidence Interval.

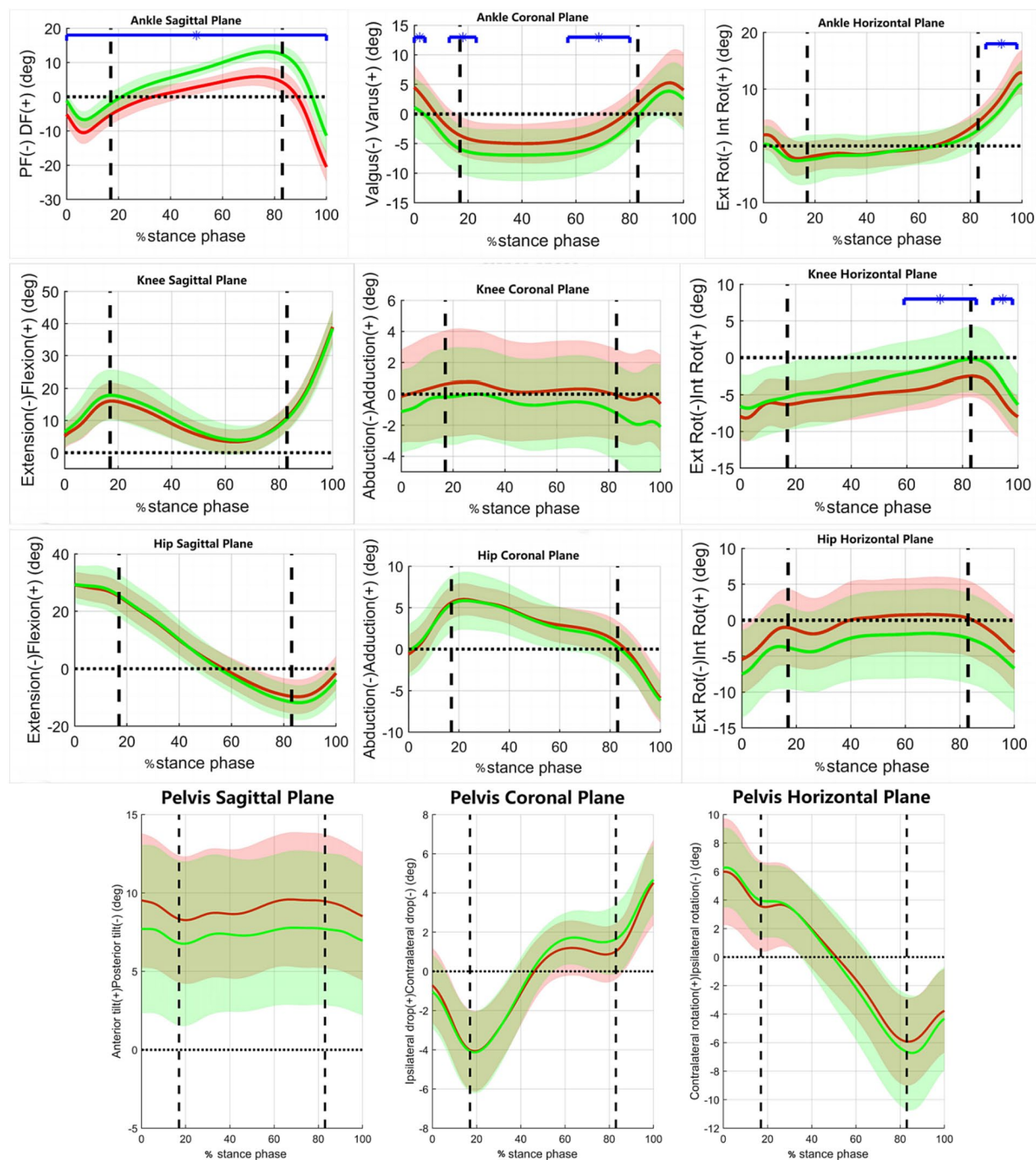


FIGURE 1

The variations of joint motion angles during walking in the two groups of subjects. x-axis, the percentage of the stance phase of gait; y-axis, Joint angles (°); Red Line, RADF group; Green Line, un-RADF group; Blue horizontal line, significant effect; DF-dorsiflexion, PF-plantarflexion; Ext Rot, External Rotation; Int Rot, Internal Rotation. First vertical dotted line, contralateral toe off; Second vertical dotted line, contralateral heel off.

3.3. Jogging

Figure 3 shows the variations in the joint motion angles of the pelvis and lower limbs in the coronal, sagittal, and horizontal planes during the stance phase of the jogging process in both groups of subjects. Figure 4 shows the variations of moments in the coronal, sagittal, and horizontal planes of each joint of the lower extremity during jogging in the two groups of subjects. Table 3 shows the results of comparing the lower limb biomechanical parameters corresponding to the moment of peak ankle dorsiflexion angle

during the stance phase, and the parameters that were significantly smaller in the RADF group than in the un-RADF group were: peak ankle dorsiflexion angle (RADF group: $17.22 \pm 3.43^\circ$, un-RADF group: $22.79 \pm 2.98^\circ$, $p < 0.01$); the anterior ground reaction force corresponding to this peak moment (RADF group: 0.02 ± 0.03 BW, un-RADF group: 0.06 ± 0.04 BW, $p < 0.01$), and the angle of pelvic ipsilateral rotation (RADF group: $0.65 \pm 2.89^\circ$, un-RADF group: $2.56 \pm 3.77^\circ$, $p < 0.05$). No significant differences were found between other biomechanical parameters of the lower extremities and the pelvis.

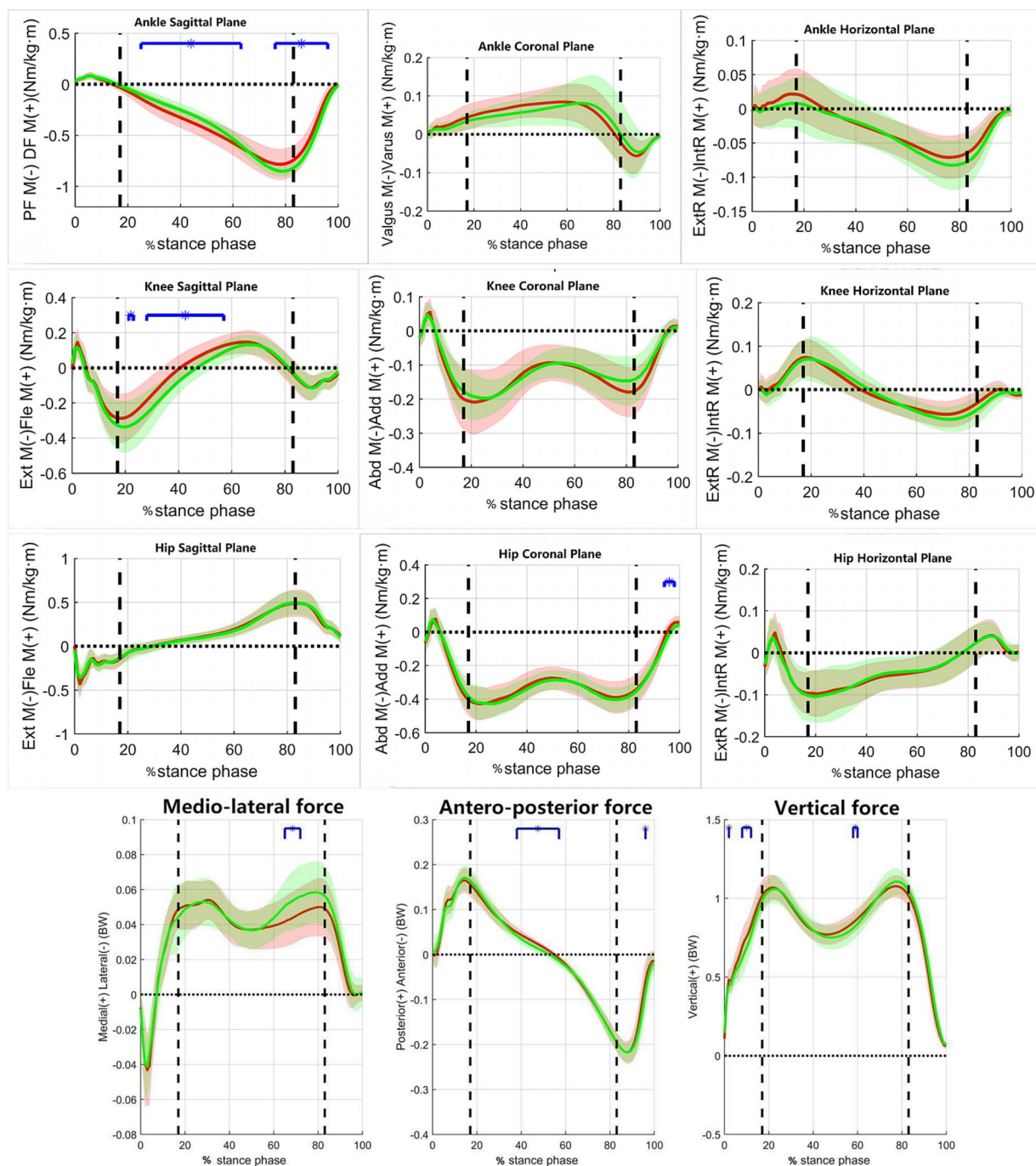


FIGURE 2

The variations of moments and ground-reaction force during walking in the two groups of subjects. x-axis, the percentage of the stance phase of gait; y-axis, the moment of force/Ground reaction force; Red Line, RADF group; Green Line, un-RADF group; Blue horizontal line, significant effect; BW, body weight; BW * BH, body weight multiplied by body height; Ext M, Extension moment; Fle M, Flexion moment; ExtR M, External Rotation moment; IntR M, Internal Rotation moment. First vertical dotted line, contralateral toe off; Second vertical dotted line, contralateral heel off.

4. Discussion

The objective of this research was to investigate the biomechanical characteristics of the lower extremity in individuals with limited ankle dorsiflexion during walking and jogging. Based on the peak ankle dorsiflexion angle during the stance phase measured in the walk test, the subjects were grouped and the differences in pelvic

kinematics and lower extremity biomechanics during walking and jogging were investigated in individuals with different peak ankle dorsiflexion angles during the stance phase of gait in the walk and jogging tests. The results showed that during walking, the angles of the pelvis, hip, knee, and ankle joints were significantly different and the dynamics of the foot and ground reaction forces in the RADF group compared with that in the un-RADF group. During jogging,

TABLE 2 Biomechanical parameters during the stance phase during walking.

Variables	un-RADF group (SD)	RADF group (SD)	t-value	p-value	Mean difference (95% CI)
Ankle					
Ankle dorsiflexion (°)	13.52 (1.96)	6.2 (2.59)	10.95	<0.001*	−7.33 (−8.67 to −5.98)
Ankle eversion (°)	2.79 (3.75)	1.88 (3.64)	0.87	0.39	0.91 (−1.20 to 3.02)
Ankle adduction (°)	0.88 (3.05)	1.08 (2.79)	−0.25	0.81	0.2 (−1.45 to 1.86)
Ankle moment					
Ankle plantarflexion moment (BW * BH)	0.84 (0.05)	0.75 (0.15)	2.53	0.02*	0.09 (0.02 to 0.16)
Ankle varus moment (BW * BH)	0.05 (0.08)	0.06 (0.05)	−0.23	0.82	0.004 (−0.03 to 0.04)
Ankle abduction moment (BW * BH)	0.08 (0.04)	0.07 (0.03)	1.23	0.22	0.01 (−0.01 to 0.03)
Knee					
Knee flexion (°)	6.84 (4.48)	6.21 (4.09)	0.53	0.6	−0.64 (−3.07 to 1.80)
Knee abduction (°)	0.84 (3.12)	−0.24 (3.08)	1.23	0.23	1.08 (−0.69 to 2.85)
Knee external rotation (°)	1.04 (4.46)	3.34 (2.84)	−2.25	0.03*	−2.30 (−4.36 to −0.25)
Knee moment					
Knee flexion moment (BW * BH)	0.06 (0.08)	0.09 (0.08)	−1.05	0.3	0.02 (−0.02 to 0.07)
Knee abduction moment (BW * BH)	0.13 (0.07)	0.15 (0.07)	−0.81	0.42	−0.02 (−0.06 to 0.02)
Knee external rotation moment (BW * BH)	0.06 (0.03)	0.05 (0.03)	1.15	0.26	0.01 (−0.01 to 0.03)
Hip					
Hip extension (°)	9.93 (6.21)	5.73 (6.72)	2.27	0.03*	4.20 (0.47 to 7.92)
Hip adduction (°)	1.13 (2.59)	2.4 (2.38)	−1.81	0.08	1.27 (−0.14 to 2.68)
Hip external rotation (°)	2.3 (6.50)	−0.46 (5.22)	1.68	0.10	2.76 (−0.54 to 6.06)
Hip moment					
Hip flexion moment (BW * BH)	0.44 (0.13)	0.37 (0.15)	1.68	0.10	−0.07 (−0.15 to 0.01)
Hip abduction moment (BW * BH)	0.39 (0.08)	0.38 (0.09)	0.56	0.58	0.01 (−0.04 to 0.06)
Hip external rotation moment (BW * BH)	0.002 (0.05)	0.02 (0.05)	−1.53	0.13	−0.02 (−0.05 to 0.01)
Pelvis					
Anterior pelvic tilt (°)	7.79 (5.07)	9.53 (4.36)	−1.32	0.19	1.74 (−0.92 to 4.41)
Pelvic ipsilateral tilt (°)	1.81 (1.66)	0.82 (1.53)	2.19	0.03*	−0.99 (−1.89 to −0.08)
Pelvis ipsilateral rotation (°)	5.96 (4.32)	4.08 (3.27)	1.77	0.08	1.88 (−0.26 to 4.01)
GRF					
Medial (BW)	0.06 (0.02)	0.05 (0.02)	2.13	0.04*	−0.01 (−0.02 to −0.001)
Anterior (BW)	0.14 (0.02)	0.1 (0.04)	3.67	0.001*	0.04 (0.02 to 0.06)
Vertical (BW)	1.09 (0.09)	1.05 (0.08)	1.83	0.07	−0.04 (−0.09 to 0.004)
Walking velocity					
V (m/s)	1.26 (0.11)	1.28 (0.10)	−0.47	0.64	0.01 (−0.05 to 0.08)

SD, standard deviation; CI, Confidence Interval; *, significant effect; BW, body weight; BW * BH, body weight multiplied by body height; GRF, ground-reaction force; Medial, medial ground reaction force; Anterior, anterior ground reaction force; Vertical, Vertical ground reaction force.

the pelvis and foot angles were significantly reduced in the RADF group.

The results showed that there was a significant difference in pelvis kinematics during walking between the RADF group and the un-RADF group in the walking test. Specifically, the angle of pelvic tilt to the ipsilateral side was significantly smaller in the RADF group than in the un-RADF group. This result suggests that important motor changes in the pelvis can exist in individuals with reduced ankle mobility. In gait, the pelvis rotates in all three planes, helping to

decrease the movement of the center of mass in the vertical and horizontal direction thus being energetically economical (29). The pelvic tilt is one of the determinants of the mediolateral displacement of the center of mass (COM) and also helps to reduce the vertical displacement of the center of gravity (30). Therefore, the reduction in the angle of ipsilateral tilt of the pelvis in the group with limited ankle dorsiflexion affects the change in the center of gravity in gait, which in turn has an impact on walking. Previous literature has reported that the horizontal plane motion of the pelvis occurs less during walking

in those with limited ankle dorsiflexion compared to those without (15), whereas the literature has rarely addressed the frontal plane motion of the pelvis, so this study extends the study of the effect of limited ankle dorsiflexion mobility on the motion of the frontal plane of the pelvis, that is the angle of the pelvis tilted to the ipsilateral side during walking was significantly less in the group with limited ankle dorsiflexion than in the non-limited group. During jogging, the angle of pelvic rotation to the ipsilateral side was significantly smaller in the group with restricted ankle dorsiflexion than in the unrestricted group ($p < 0.05$). The results suggest that individuals with smaller ankle dorsiflexion angles will have less movement in the horizontal plane of the pelvis during exercise, and a previous study (31) has shown that the smaller the pelvic rotation relative to the supporting foot during the support phase of gait, the greater the torsional stress on the lower extremity, which correlates more with lower extremity injury (32).

The RADF group had a significantly lower hip extension angle in the walking test. It was indicated that limitation of ankle dorsiflexion was significantly associated with limitation of hip extension during walking. Peak ankle dorsiflexion occurs at the moment of heel lift at the end of the stance phase of gait when the hip is in extension (33). Ankle push-off contributes to leg swing and propels the body over the supporting lateral limb (24), while a decrease in peak ankle dorsiflexion may decrease ankle stirrup strength and hip extension. Meanwhile, hip extension more appropriately loads the ankle in dorsiflexion, creating better muscular and mechanical energy, which is essential for stance-to-swing transition and thus forward propulsion (34). Therefore, the results of this study suggest that a reduction in peak ankle dorsiflexion affects the movement of the sagittal plane of the hip joint, which in turn adversely affects the transition from the stance to the swing phase in gait.

Differences in knee motion during walking were observed between the two groups of subjects, with the RADF group having a significantly greater angle of external knee rotation. The external rotation of the knee that occurs at the end of the support phase can be explained according to the “screw-home mechanism” (35), where the final extension of the knee during the gait cycle is normally accompanied by the external rotation of the tibia relative to the femur. In contrast, the RADF group showed greater external knee rotation at the moment of peak ankle dorsiflexion. When the knee joint is extended, the anterior cruciate ligament (ACL) gets tangled and tightened if the tibia is rotated externally with respect to the femur (screw-home movement) (36), which may increase the risk of ACL injury. This is because the ACL not only prevents knee hyperextension but also stabilizes the knee against tibial rotation (37). Many researchers have reported that knee rotation is significantly associated with ACL injury (38–41) and that external knee rotation combined with knee abduction may cause the ACL to impinge on the femoral condyle, which in turn increases the load on the ACL (42). Therefore, greater external knee rotation angles in individuals with limited ankle dorsiflexion may increase the risk of a knee injury. However, no changes in knee biomechanical parameters other than knee external rotation angle were found in this study, which is not consistent with the hypothesis of this study and the results in the literature (15, 43) and may be related to the different grouping methods and inter-subject differences.

In the present study, during the walking test, the RADF group had a smaller ankle dorsiflexion moment. Meanwhile, the RADF group

also had smaller anterior ground reaction forces in both walking and jogging test. In gait, the body is propelled forward mainly through plantar flexion of the stirrups off the ground to generate thrust (32). In contrast, the plantarflexion push-off moment of the ankle joint is generated by the triceps calf muscle (biceps, medial and lateral gastrocnemius) and other external foot muscle-tendon units. And the peak ankle push-off force is partially derived from the release of elastic energy stored in the Achilles tendon during ankle dorsiflexion (44). The results of the study showed that a restricted ankle dorsiflexion angle reduces the ankle plantarflexion moment, which suggests that individuals with restricted ankle dorsiflexion have less ability to swing their lower limbs forward during walking. Also, this may account for the less forward ground reaction force in the RADF group during walking versus jogging. From the results, it was observed that the anterior ground reaction force of walking was greater than that of jogging, which may be caused by changes in gait parameters due to changes in movement patterns during the transition from walking to running, such as the duration of the stance phase and the change in stride frequency, as well as the choice of walking versus jogging speed that equally affects the magnitude of the ground reaction force, which is consistent with the results of previous studies in the literature (45). Since the medial-lateral forces have particularly high coefficients of variation (46–48), they are the least reliable among the ground reaction forces and therefore are not analyzed in this study for the time being.

5. Strengths and limitations

In this study, a three-dimensional motion capture system is proposed to determine whether subjects have sufficient ankle dorsiflexion angle to complete functional movements such as walking and jogging. This study also systematically analyzed the biomechanical effects of different ankle dorsiflexion angles on hip, knee, ankle and pelvis during walking and jogging.

The present study has several limitations. Based on the maximum dorsiflexion angle in walking test, this study proposed a novel method of diagnosing functional limited ankle dorsiflexion by maximum ankle dorsiflexion during stance phase of walking. However, this method was not further compared with other methods such as the weight-bearing lunge test, which may affect the validity of this method. This study focused on and discussed lower extremity biomechanics and pelvic motion during walking versus jogging in individuals with ankle dorsiflexion restrictions, but did not further compare the differences between walking and jogging in individuals with ankle dorsiflexion restrictions. Jogging requires a greater ankle dorsiflexion angle to propel the body forward, but the transition from walking to running shortens the duration of the support period of gait (38), which can affect the biomechanics of the lower extremity during the gait cycle and needs to be continued to be explored in future studies. In addition, lower extremity muscle activity or muscle strength was not assessed as a variable in this study and needs to be further advanced in future studies. Finally, due to the lack of upper limb model construction, the COM could not be determined, and the changes of the COM in individuals with different ankle dorsiflexion angles during walking and jogging should be further studied.

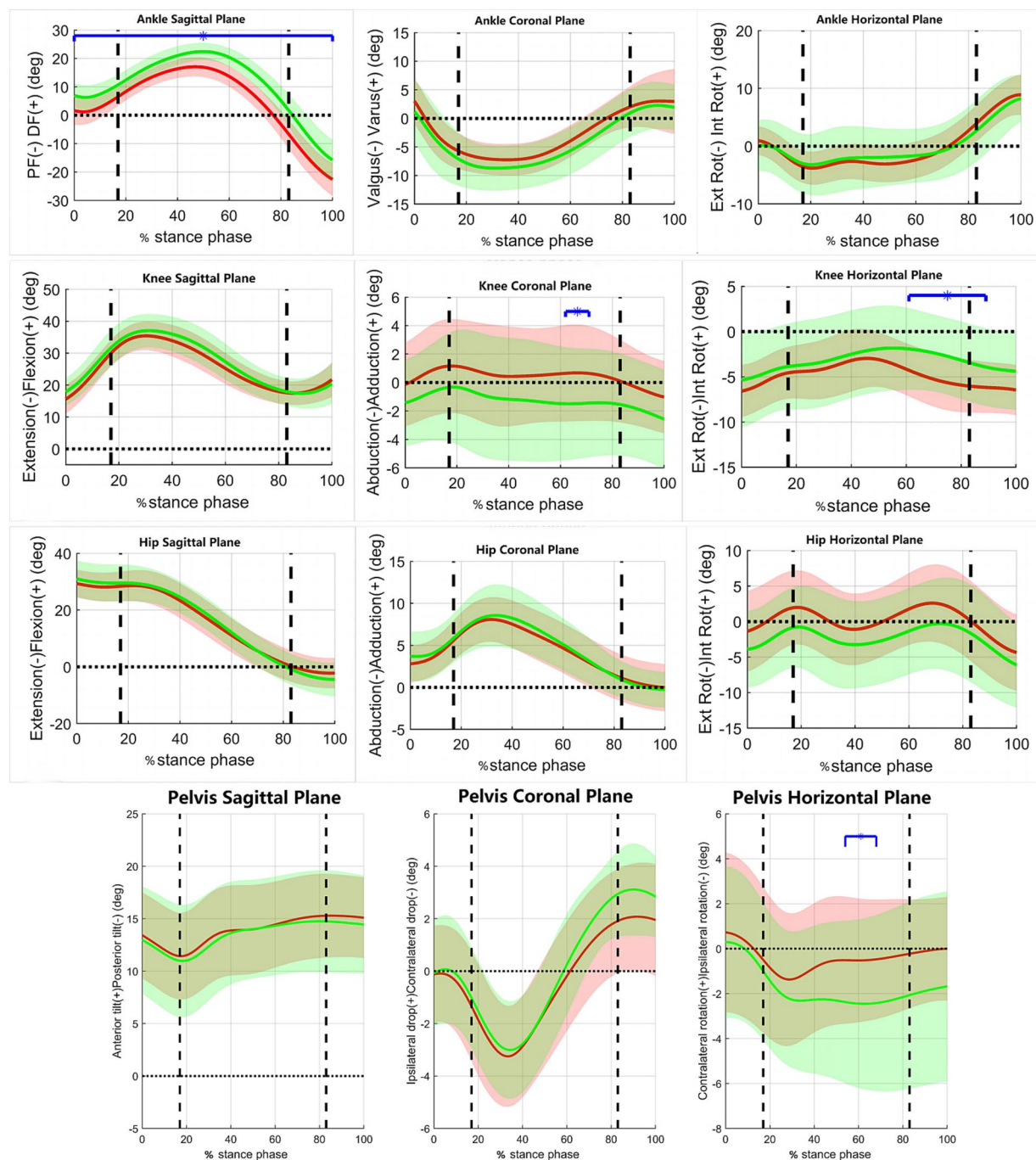


FIGURE 3

The variations of joint motion angles during jogging in the two groups of subjects. x-axis, the percentage of the stance phase of gait; y-axis, Joint angles (°); Red Line, RADF group; Green Line, un-RADF group; Blue horizontal line, significant effect; DF-dorsiflexion, PF-plantarflexion; Ext Rot, External Rotation; Int Rot, Internal Rotation. First vertical dotted line, contralateral toe off; Second vertical dotted line, contralateral heel off.

6. Conclusion

The present study demonstrated that during walking, individuals with smaller ankle dorsiflexion peaks in gait result in reduced pelvic frontal plane motion; reduced hip posterior extension at the moment of peak ankle dorsiflexion, increased knee external rotation angle, and

reduced ankle plantarflexion moment and anterior ground reaction force. During jogging, ipsilateral pelvic rotation and anterior ground reaction forces were reduced in those with limited ankle dorsiflexion. Thus, limited ankle dorsiflexion alters the movement pattern of the lower extremity during walking and jogging, diminishing the body's ability to propel forward, which may lead to higher injury risks.

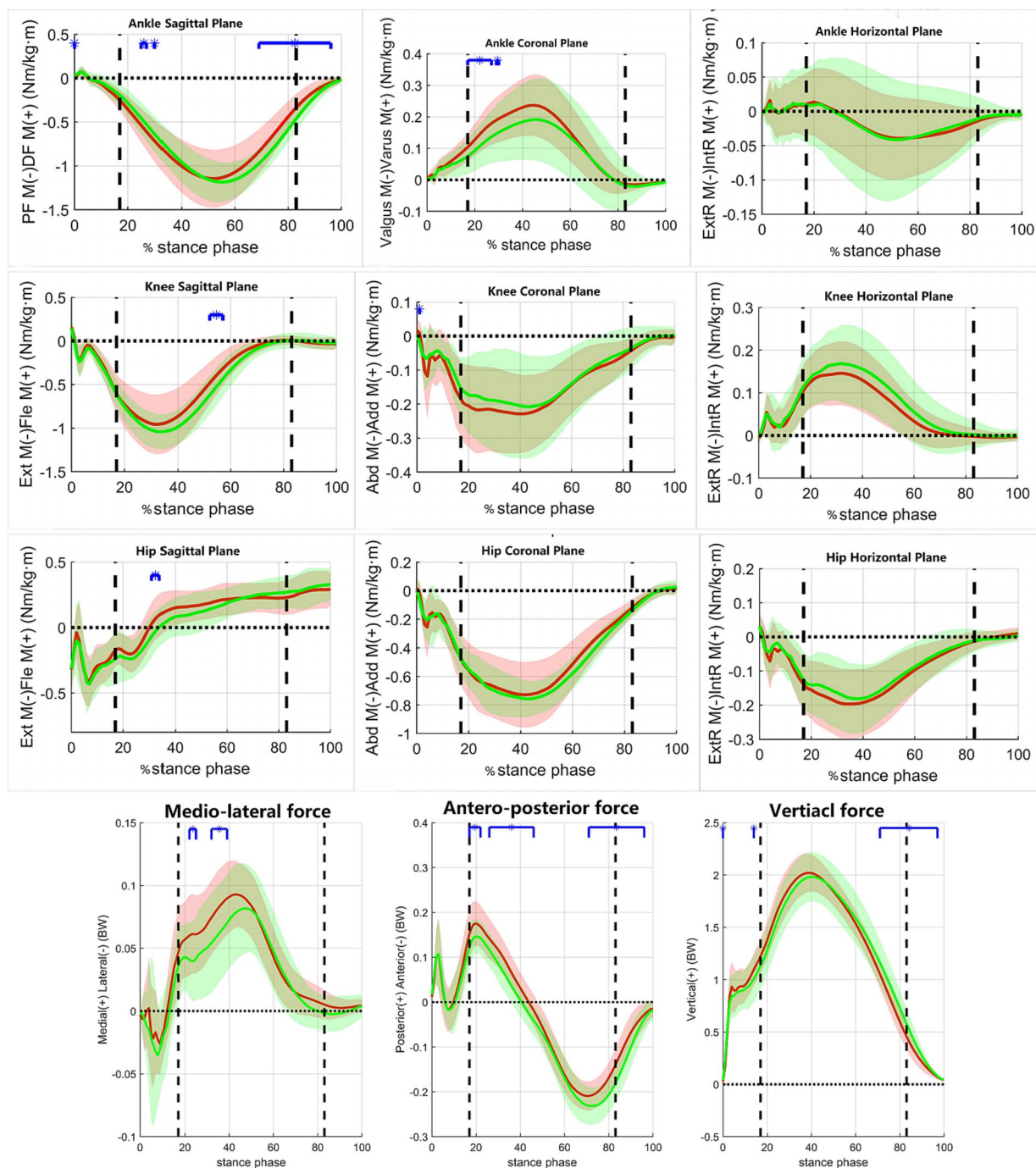


FIGURE 4

The variations of moments and ground-reaction force during walking in the two groups of subjects. x-axis, the percentage of the stance phase of gait; y-axis, the moment of force/Ground reaction force; Red Line, RADF group; Green Line, un-RADF group; Blue horizontal line, significant effect; BW, body weight; BW * BH, body weight multiplied by body height; Ext M, Extension moment; Fle M, Flexion moment; ExtR M, External Rotation moment; IntR M, Internal Rotation moment. First vertical dotted line, contralateral toe off; Second vertical dotted line, contralateral heel off.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Peking University Third Hospital. The studies were conducted in accordance with the local legislation and institutional

TABLE 3 Biomechanical parameters during the stance phase during jogging.

Variables	un-RADF group (SD)	RADF group (SD)	t-value	p-value	Mean difference (95% CI)
Ankle					
Ankle dorsiflexion (°)	22.79 (2.98)	17.22 (3.43)	6.01	<0.001*	−5.57 (−7.43 to −3.71)
Ankle eversion (°)	7.74 (3.85)	6.69 (2.89)	1.05	0.30	1.04 (−0.97 to 3.06)
Ankle abduction (°)	2.02 (5.15)	2.92 (3.24)	−0.71	0.48	−0.90 (−3.49 to 1.69)
Ankle moment					
Ankle plantarflexion moment (BW * BH)	1.16 (0.20)	1.13 (0.33)	0.39	0.70	0.03 (−0.13 to 0.19)
Ankle varus moment (BW * BH)	0.19 (0.14)	0.23 (0.10)	−1.30	0.20	0.04 (−0.02 to 0.11)
Ankle adduction moment (BW * BH)	0.04 (0.09)	0.04 (0.06)	−0.17	0.86	−0.004 (−0.05 to 0.04)
Knee					
Knee flexion (°)	32.51 (5.40)	31.56 (4.87)	0.65	0.52	−0.94 (−3.86 to 1.97)
Knee abduction (°)	1.42 (4.38)	−0.4 (3.38)	1.68	0.10	1.82 (−0.36 to 4.00)
Knee external rotation (°)	2.2 (4.77)	2.94 (3.08)	−0.62	0.54	−0.74 (−3.15 to 1.67)
Knee moment					
Knee flexion moment (BW * BH)	0.7 (0.20)	0.66 (0.27)	0.54	0.59	0.04 (−0.10 to 0.18)
Knee abduction moment (BW * BH)	0.19 (0.15)	0.23 (0.11)	−1.00	0.33	−0.04 (−0.11 to 0.04)
Knee internal rotation moment (BW * BH)	0.12 (0.09)	0.1 (0.07)	0.83	0.41	−0.02 (−0.06 to 0.03)
Hip					
Hip flexion (°)	18.66 (5.36)	19.23 (5.77)	−0.36	0.72	0.57 (−2.64 to 3.78)
Hip adduction (°)	6.86 (3.19)	6.78 (2.73)	0.09	0.93	−0.08 (−1.75 to 1.60)
Hip external rotation (°)	2.81 (6.19)	0.65 (4.93)	1.38	0.17	2.15 (−0.98 to 5.29)
Hip moment					
Hip flexion moment (BW * BH)	0.14 (0.13)	0.16 (0.12)	−0.60	0.55	0.02 (−0.05 to 0.09)
Hip abduction moment (BW * BH)	0.74 (0.13)	0.73 (0.22)	0.20	0.84	0.01 (−0.10 to 0.12)
Hip external rotation moment (BW * BH)	0.14 (0.09)	0.17 (0.09)	−1.26	0.21	−0.03 (−0.09 to 0.02)
Pelvis					
Anterior pelvic tilt (°)	14 (4.67)	13.99 (4.31)	0.01	0.99	−0.01 (−2.56 to 2.54)
Pelvic ipsilateral tilt (°)	1.36 (1.89)	2.15 (1.88)	−1.48	0.14	−0.80 (−1.87 to 0.28)
Pelvis ipsilateral rotation (°)	2.56 (3.77)	0.65 (2.89)	2.04	0.047*	1.91 (0.03 to 3.78)
GRF					
Medial (BW)	0.09 (0.03)	0.09 (0.03)	−1.06	0.30	0.01 (−0.01 to 0.02)
Anterior (BW)	0.06 (0.04)	0.02 (0.03)	3.84	<0.001*	0.04 (0.02 to 0.06)
Vertical (BW)	1.86 (0.27)	1.92 (0.17)	−1.04	0.30	0.06 (−0.06 to 0.19)
Jogging velocity					
V (m/s)	2.39 (0.15)	2.30 (0.17)	1.80	0.08	−0.08 (−0.18 to 0.01)

SD, standard deviation; CI, Confidence Interval; *, significant effect; BW, body weight; BW * BH, body weight multiplied by body height; GRF ground-reaction force; Medial, medial ground reaction force; Posterior, Posterior ground reaction force; Vertical, Vertical ground reaction force.

requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YR: Writing – review & editing, Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Project administration, Software, Supervision, Validation. NY: Writing – original draft, Data

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Conflict of interest

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Diving into progress: a review on current therapeutic advancements in spinal muscular atrophy

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Spinal muscular atrophy (SMA) is an uncommon disorder associated with genes characterized by the gradual weakening and deterioration of muscles, often leading to substantial disability and premature mortality. Over the past decade, remarkable strides have been made in the field of SMA therapeutics, revolutionizing the landscape of patient care. One pivotal advancement is the development of gene-targeted therapies, such as nusinersen, onasemnogene abeparvovec and risdiplam which have demonstrated unprecedented efficacy in slowing disease progression. These therapies aim to address the root cause of SMA by targeting the survival motor neuron (SMN) gene, effectively restoring deficient SMN protein levels. The advent of these innovative approaches has transformed the prognosis for many SMA patients, offering a glimmer of hope where there was once limited therapeutic recourse. Furthermore, the emergence of small molecule compounds and RNA-targeting strategies has expanded the therapeutic arsenal against SMA. These novel interventions exhibit diverse mechanisms of action, including SMN protein stabilization and modulation of RNA splicing, showcasing the multifaceted nature of SMA treatment research. Collective efforts of pharmaceutical industries, research centers, and patient advocacy groups have played an important role in expediting the translation of scientific discoveries into visible clinical benefits. This review not only highlights the remarkable progress achieved in SMA therapeutics but also generates the ray of hope for the ongoing efforts required to enhance accessibility, optimize treatment strategies, rehabilitation (care and therapies) and ultimately pave the way for an improved quality of life for individuals affected by SMA.

KEYWORDS

spinal muscular atrophy, survival motor neuron, rehabilitation, nusinersen, onasemnogene abeparvovec, risdiplam

1 Introduction

Spinal muscular atrophy (SMA) is a rare and debilitating genetic disorder that primarily exerts influence on the motor neurons in the spinal cord, leading to muscle atrophy and weakness. This disorder has garnered significant attention in recent years due to the development of groundbreaking treatments, such as gene therapies, which have the potential

to change the prognosis for individuals affected by SMA (1). SMA is a heterogeneous group of inherited neuromuscular disorders characterized by the progressive degeneration of motor neurons in the spinal cord. The condition's prevalence and incidence can vary significantly based on geographic and ethnic factors, making it a complex subject for epidemiological study (2). The estimated global prevalence of SMA ranges from 1 in 6,000 to one in 10,000 live births, with variations in different populations and regions. This range represents a significant burden for affected families and healthcare systems (3). This condition is an autosomal recessive disorder resulted by mutations in the survival motor neuron 1 (*SMN1*) gene. The incidence of SMA depends on the carrier frequency of these mutations in a given population (4). SMA is classified into different divisions based on the age of onset and clinical severity, which also have implications for epidemiology. SMA type I, with an early outbreak and severe phenotype, is often the most common, while SMA type IV, with adult onset and milder symptoms, is rarer (5). There may be variations in the prevalence and incidence of SMA across different countries and regions. For example, some studies suggest a higher prevalence in certain European populations. Research is ongoing to understand these variations better (6). Addressing the impact of SMA on families and healthcare systems necessitates a multifaceted approach that includes comprehensive support services, caregiver education and training, psychosocial interventions, financial assistance programs, and healthcare system reforms to improve access to specialized care (7, 8). Collaboration among healthcare providers, lawmakers, advocacy organizations, and community stakeholders is critical for reducing the effect of SMA and improving the well-being of afflicted individuals and their families (9). In this review, we discussed the epidemiology and clinical classification of SMA, shedding light on the latest research, rehabilitation and clinical findings.

2 Clinical classification of SMA

In 1891, SMA first came to light through the observations of Guido Werdnig in two infant brothers (10). Over the subsequent nine years, Johann Hoffmann documented an additional seven cases. The traditional framework for classifying SMA was built upon the timing of symptom onset and the highest level of motor function achieved. While the cases they scrutinized had intermediate symptom severity, the term “Werdnig-Hoffmann disease” was coined to denote the more severe manifestations of SMA (11). The year 1899 saw Sylvestre and Beevor describe severe forms of SMA, further delineating the spectrum. In 1964, Dubowitz contributed to the field by detailing intermediate forms of SMA in 12 patients and naming this variant “Dubowitz disease” (11–13). Additionally, in 1955, the discovery of a milder form of SMA was made, with Kugelberg and Welander providing a comprehensive description one year later (14). This division of kinds of SMA is based on the age of symptom when it starts, the highest motor function achieved, and the severity of muscle weakness. Research into the epidemiology of SMA is vital for understanding the wide prevalence of disease, its occurrence, and natural evolution. These studies provide beneficial insights into the biological, ecological, and demographic factors that drive the development and progression of SMA in populations. The International Standard of Care Committee for SMA (ISCCSMA) has

classified SMA into five primary types, as shown in the Figure 1, which include:

2.1 SMA type 0

This is the most drastic and rarest form of SMA, with onset in womb or within the first few days of life. Neonate with SMA type 0 often exhibit severe muscle weakness and may not survive beyond a few months (15).

2.2 SMA type I (Werdnig-Hoffmann disease)

This is the most common form of SMA. Symptoms typically appear before first six months of life, and affected newborn may never will have the ability to sit independently or stand. SMA type I is characterized by severe muscle weakness, respiratory difficulties, and a shortened lifespan if not treated (16).

2.3 SMA type II

This form of SMA has a later onset, typically occurring between six and eighteen months of age. Affected individuals often get the ability to sit but may struggle with standing or walking. The rate of disease progression varies among individuals (12).

2.4 SMA type III (Kugelberg–Welander disease)

This type of disorder has an onset after 18 months of age. Individuals with this form may achieve the ability to walk independently, but muscle weakness and atrophy progress slowly. Some individuals may experience a relatively normal lifespan (17).

2.5 SMA type IV

This is the mildest form of SMA, with an adult onset of symptoms. Affected individuals may experience muscle weakness, twitching, and exercise intolerance. The progression of the disorder is slow, and life aging is normal (18). Twenty cases with SMA type 4 were found in a Brazilian cohort of 227 SMA patients. This study includes the biggest cohort of SMA type 4 patients and provides practical, genetic, radiological, and neurophysiological aspects that may serve as biomarkers for future SMA-specific genetic therapeutics (19).

3 Genetics of spinal muscular atrophy

The *SMN1* gene encodes the survival motor neuron (SMN) protein, which is essential for the normal functioning of motor neurons in the spinal cord (20, 21). SMN, a foundational protein within the SMN-Gemin multiprotein complex, serves as a core component. Additionally, it actively engages in various physiological functions, including responding to cellular stress, facilitating axon

Natural History

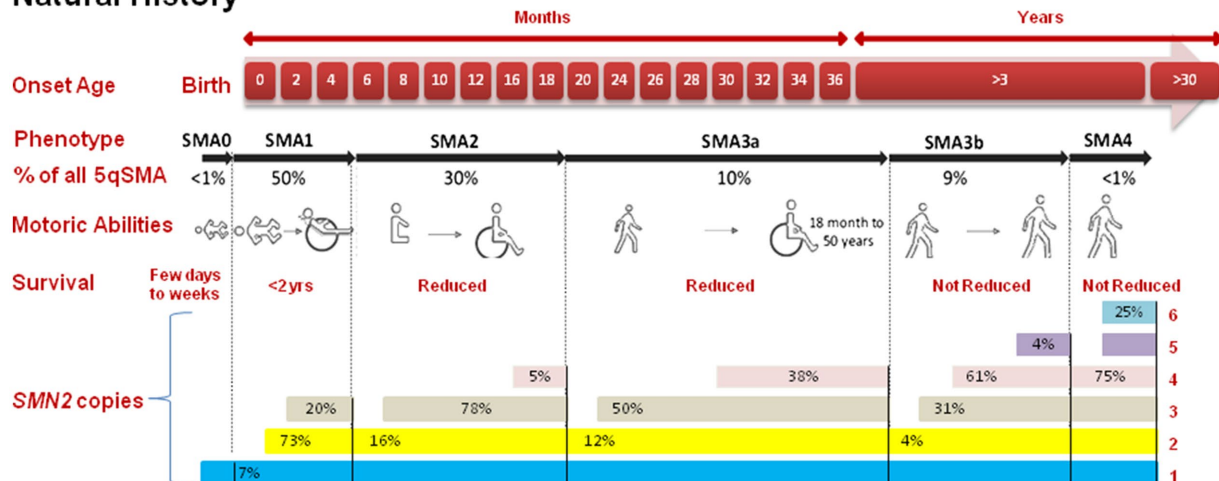


FIGURE 1

Comprehensive insight into the progression of SMA. The top panel categorizes the five types of SMA (0, 1, 2, 3, 4) which is based on the onset age and achieved motor capabilities. SMA type 3 is further subdivided upto 3a (onset <3 years) and 3b (onset >3 years). Furthermore, the figure presents the total count of *SMN2* gene copies for each SMA type.

transport, regulating cytoskeletal dynamics, modulating mitochondrial and bioenergy pathways, and participating in ubiquitin pathways. Consequently, SMN emerges as a significant molecule, intricately involved in a multitude of essential activities that underpin human existence (22). These *SMN* genes are found within the 5q13 region, which harbors inverted repeats and multiple gene copies (20, 23, 24). The telomeric version of *SMN1*, with its nine exons, generates a functional 294-amino acid, 38kDa SMN protein as shown in Figure 2. Typically, this protein is found in both organelles that is the cytoplasm and nucleus, specifically in the Gemini of coiled bodies compartment, which forms Cajal bodies holding high concentrations of small ribonucleoproteins (snRNPs) along with pre-mRNAs (25). SMN contains crucial and highly conserved domains that are essential for its cellular functions. Any kind of mutations occurring within these domains of *SMN1* result in the production of an inefficient protein (26). The *SMN2* is a centromeric gene which is a paralog of *SMN1*, having almost identical sequences with *SMN1* except for 5 nucleotide differences. To understand the contributions of the survival motor neuron 2 (*SMN2*) gene to spinal muscular atrophy (SMA) pathology, it's important to grasp its differences in alternative splicing compared to *SMN1* and how these differences impact disease severity and progression. The one of these changes leads to the exclusion of exon number 7 in approximately 90% of the transcripts through alternative splicing (27). *SMN2* is located 875 kb far from *SMN1* and originates from a duplication of an ancestral gene which is unique to the human lineage (28). Both *SMN1* and *SMN2* genes encode the survival motor neuron (SMN) protein, which is crucial for the survival and function of motor neurons. However, a critical difference between *SMN1* and *SMN2* lies in a single nucleotide difference within exon 7, resulting in a C-to-T transition in *SMN2*. This single nucleotide change in *SMN2* affects the alternative splicing pattern, leading to the exclusion (skipping) of exon 7 in a significant proportion of transcripts. Exon 7 skipping results in the production of an isoform of the SMN protein lacking exon 7 (SMNΔ7), which is less stable and less functional compared to the full-length SMN protein produced by

SMN1. The exclusion of exon 7 in a substantial portion of *SMN2* transcripts results in reduced levels of functional SMN protein in cells, contributing to the pathogenesis of SMA. While *SMN2* can partially compensate for the loss of *SMN1* function, the lower levels of full-length SMN protein produced by *SMN2* are insufficient to fully support motor neuron survival and function. The severity and progression of SMA are influenced by the number of copies of *SMN2* present in the genome. Individuals with fewer copies of *SMN2* typically produce lower levels of functional SMN protein and tend to have more severe forms of the disease, whereas those with more copies of *SMN2* may produce higher levels of functional SMN protein and exhibit milder symptoms. The unique alternative splicing pattern of *SMN2* has made it a primary target for therapeutic interventions aimed at increasing the production of full-length SMN protein. SMA symptoms manifest when there is a deficiency of proper functional SMN protein, usually stemming from minimum one copy of the *SMN1* (29). However, around 10% of full-length *SMN2* transcripts, often present in multiple copies within the genome, provide some degree of protection against motor neuron degeneration (30). The more *SMN2* copies a patient possesses, the more they can compensate for the absence of *SMN1* (31). Consequently, in rare cases, individuals with 6 or more copies can exhibit milder symptoms appearing after the age of 30, characterized by mild muscle weakness and retained full mobility. Most type I SMA patient's carries either one or two *SMN2* copies (32). While the number of *SMN2* gene copies strongly correlates with disease severity, some studies suggest that it may not always be a definitive indicator of severity, especially in SMA patients who retain one *SMN1* allele (33). Additionally, even when *SMN* is expressed normally, point mutations in *SMN* can affect protein functionality and stability, leads to the disorder, along with genetic and epigenetic factors, as well as environmental influences, may modulate disease (34). Approaches such as antisense oligonucleotide (ASO) therapy and small molecule drugs target the splicing machinery to promote the inclusion of exon 7 in *SMN2* transcripts, thereby increasing the production of functional SMN protein. These therapies aim to

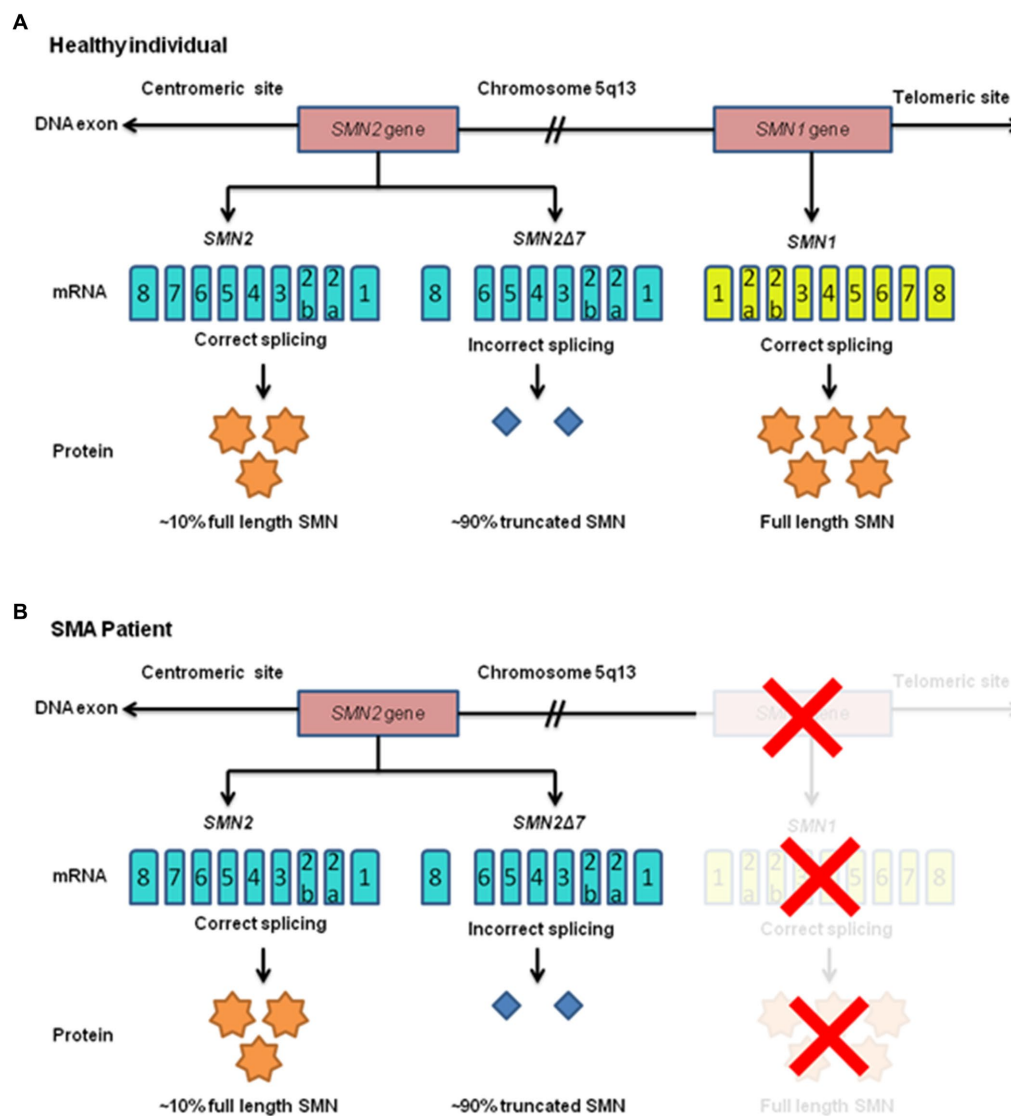


FIGURE 2

Human survival motor neuron (SMN) gene expression is shown in a schematic diagram for both healthy people and those with SMA. The chromosome 5q13 region (long arm of chromosome 5) has been explicitly identified as the location of the telomeric *SMN1* and centromeric *SMN2* genes. Full-length, functional SMN (FL-SMN) protein is produced by the *SMN1* gene whereas the *SMN2* gene, owing to incorrect splicing, produces 90% truncated SMN protein (SMN2Δ7) and only 10% of FL-SMN protein. (A) Both SMN genes are present in healthy individuals. (B) The *SMN1* gene is absent in SMA patients due to mutations, which prevent *SMN1* from producing FL-SMN protein (this condition is denoted by a red "X"). Because production is completely dependent on the *SMN2* gene, there is inadequate production.

augment the levels of functional SMN protein in motor neurons, potentially ameliorating disease symptoms and improving outcomes for individuals with SMA.

4 Molecular mechanisms of SMA

The underlying molecular mechanisms of SMA revolve around the loss of functional SMN protein and its impact on motor neurons and muscle cells. The reduction in functional SMN protein in motor neurons results in their degeneration (35). Motor neurons are responsible for transmitting signals from the spinal cord to muscles, and without proper functioning SMN protein, these neurons become

vulnerable to damage and eventual death. This leads to muscle weakness and atrophy (36). SMN protein plays a crucial role in the assembly of snRNPs, which are essential for mRNA splicing (37). Impaired snRNP assembly due to SMN deficiency leads to widespread splicing defects in various genes, further exacerbating motor neuron dysfunction (38). While SMA is primarily a disorder of motor neurons, the resulting muscle atrophy and weakness are critical clinical features. The lack of neural input from affected motor neurons causes muscle disuse, contributing to muscle wasting (39). The neuromuscular junction, where motor neurons communicate with muscle cells, is also affected in SMA (40). The loss of functional motor neurons disrupts this communication, leading to muscle weakness and contractures (41).

5 Diagnostic approaches of spinal muscular atrophy

SMA presents with a spectrum of clinical features, ranging from severe, early-onset forms to milder, adult-onset forms. The key clinical manifestations include muscle weakness, atrophy, and hypotonia. Patients with SMA may also exhibit respiratory difficulties, joint contractures, and scoliosis (42). It is essential to recognize these clinical signs early, as timely intervention can significantly impact the prognosis and quality of life for affected individuals.

5.1 Clinical evaluation

A thorough clinical evaluation is the initial step in diagnosing SMA. The healthcare provider takes a detailed medical history, conducts a physical examination, and assesses motor function (43). The clinical evaluation includes a review of family history to identify any known cases of SMA or related neuromuscular disorders. It is important to consider that SMA may not be the first suspicion in cases with mild or atypical symptoms (44).

5.2 Electromyography

Electromyography (EMG) is a diagnostic technique used to assess the electrical activity of muscles and nerves (45). In SMA, EMG may reveal neurogenic changes, denoting motor neuron dysfunction. EMG can help distinguish SMA from other neuromuscular disorders and provide information about the extent of motor neuron involvement (46).

5.3 Nerve conduction studies

Nerve conduction studies (NCS) evaluate the function of peripheral nerves. In SMA, NCS can be normal or show mild abnormalities. These tests help rule out other neurological conditions and provide additional information to support the diagnosis of SMA (47).

5.4 Muscle biopsy

While muscle biopsy is not the primary diagnostic tool for SMA, it can be used to confirm the absence of muscle pathology, ruling out conditions like muscular dystrophy. Muscle biopsies typically show atrophy and denervation in SMA, supporting the diagnosis (48).

5.5 Serum creatine kinase levels

Measuring serum creatine kinase (CK) levels can be useful in differentiating SMA from muscular dystrophies. In SMA, CK levels are usually within the normal range or only mildly elevated, whereas in muscular dystrophies, CK levels are significantly elevated (49).

5.6 Newborn screening

Newborn screening for spinal muscular atrophy (SMA) is a critical and rapidly evolving aspect of pediatric healthcare aimed at early detection and intervention for this devastating genetic disorder. One of the primary benefits of newborn screening for SMA is the early identification of affected infants. Unlike in the past, when diagnosis often occurred after the onset of symptoms, newborn screening allows for early intervention and treatment (50).

5.7 Genetic testing

Genetic testing is the gold standard for diagnosing SMA. It provides a definitive diagnosis, identifies the specific genetic mutation, and helps determine the severity of the condition. Genetic testing typically involves the following approaches: (a) the primary genetic test for SMA involves analyzing the *SMN1* gene. Most SMA cases result from deletions or mutations in this gene, leading to reduced SMN protein levels. This test is highly specific and sensitive and can diagnose SMA with a high degree of accuracy (51). (b) In addition to *SMN1* analysis, counting the number of copies of the *SMN2* gene can provide information about the disease severity. SMA patients with more *SMN2* copies tend to have milder forms of the disease, while those with fewer copies typically have more severe forms (52).

5.8 Next-generation sequencing

Next-generation sequencing (NGS) is a powerful tool for identifying rare or typical mutations in the *SMN1* gene. It can be especially useful in cases where standard genetic tests do not yield a diagnosis. NGS can also detect other rare genetic conditions that may mimic SMA (53).

5.9 Prenatal testing

Genetic testing can be performed during pregnancy to identify SMA in the fetus. This can be done through chorionic villus sampling or amniocentesis. Early diagnosis allows for informed reproductive decisions and early intervention if the fetus is affected (54). Prenatal testing for spinal muscular atrophy (SMA) raises several ethical considerations, including issues related to informed consent, autonomy, disability rights, and the potential for discrimination. It's crucial that expectant parents fully understand the purpose, benefits, limitations, and potential consequences of SMA prenatal testing. They should have access to comprehensive information about SMA, including its prognosis, available treatments, and the emotional impact of receiving a positive result. Current recommendations by the American College of Medical Genetics (ACMG) include offering SMA carrier screening to all couples, regardless of race or ethnicity, before conception or early in pregnancy. Current recommendation by the American Congress of Obstetricians and Gynecologists (ACOG) do not advise preconception and prenatal screening for SMA be offered to the general population and advice testing offered to general population (55). Some disability rights advocates argue that prenatal testing for conditions like SMA perpetuates ableism and sends a

message that individuals with disabilities have less value or are not worthy of existence. This perspective challenges the notion that certain disabilities should be actively prevented or eliminated through selective abortion.

6 Disease-modifying treatments and current implications

There are several treatments approaches for the SMA such as (Table 1).

Nusinersen (marketed as Spinraza®) was the first FDA-approved disease-modifying treatment for SMA having obtained approval in December 2016 and by the EMA in 2017 for both infant and adult (56). This innovative therapeutic approach, which involves the intrathecal administration of a 2'-O-methoxyethyl phosphorothioate modified antisense oligonucleotide (ASO), focuses on enhancing the incorporation of exon 7 into mRNA transcripts of *SMN2* (57). The intrathecal route of administration is crucial for nusinersen's effectiveness in treating SMA because it allows for targeted delivery to the site of pathology, bypasses the blood-brain barrier, optimizes concentration at the target site, minimizes systemic side effects, and provides a longer duration of action within the central nervous system (57). By administering nusinersen directly into the central nervous system (CNS) through the intrathecal route, the medication effectively suppresses the activity of certain splice-factors and binds to a specific intronic splice-silencing site within intron 7 of *SMN2* (58). This intervention substantially increases the probability of exon 7 being included in the mRNA, ultimately enabling the translation of a more substantial quantity of fully functional SMN protein (27). This enhanced production has demonstrated significant improvements in both survival and the overall condition of various experimental models of SMA. Importantly, nusinersen's journey to approval and commercialization has been bolstered by a multitude of studies confirming its efficacy, without any notable drug-related adverse events (59). Due to ASOs' inability to traverse the blood-brain barrier, nusinersen was consistently administered intrathecally in all clinical trials. During the initial loading phase, it was administered four times over two months, and in the maintenance phase, it was given once

every four months (60). The standard dosage of nusinersen typically amounts to 12 milligrams (61). Studies on nusinersen have revealed the potential for some patients to regain lost abilities, such as sitting up, standing, and walking, without the need for therapy. Furthermore, early initiation of this treatment has demonstrated positive outcomes in individuals with SMA types I, II, and III (62). It is worth noting that a notable drawback of this therapy is the possibility of side effects, including constipation and upper and lower respiratory tract infections (63).

Onasemnogene abeparvovec (Zolgensma), an advanced gene therapy: In May 2019, the FDA granted approval to AVXS-101, also known as Zolgensma is a gene therapy approved for the treatment of SMA, developed by AveXis, a subsidiary of Novartis (56). This approval followed the release of favorable outcomes from the phase one clinical trial known as START (Identifier: NCT01547871). This trial assessed the drug's safety and effectiveness when administered as a one-time infusion to infants with SMA symptoms appearing before six months of age. Subsequently, in March 2020, Zolgensma received conditional marketing authorization, and in May 2020, it was granted approval by the European Medicines Agency (EMA) as well (Zolgensma, 2020a; Novartis, 2020) (64). The adeno-associated virus 9 (AAV9) capsid is used to transport the SMN-encoding complementary DNA (cDNA) to the motor neurons that need it (65–67). A single dose of AAV9 administered intravenously (IV) is sufficient to transport a functional copy of the *SMN1* gene over the blood-brain barrier and into patient cells, where it may stimulate the production of SMN protein (27). The *SMN1* trans gene and synthetic promoter based on AAV9 are also crucial components in maintaining SMN protein synthesis throughout time (68). Although it successfully corrects the underlying molecular defect in SMA, it has a deleterious effect on the liver by elevating serum amino transferase (69). However, prednisone is effective at reducing elevated liver enzymes. Therefore, at least three months after administration, patients should be monitored for liver function (70, 71). The long-term durability of the benefits of Zolgensma (onasemnogene abeparvovec) is still being actively studied and monitored. Zolgensma is a gene therapy approved for the treatment of spinal muscular atrophy (SMA) in pediatric patients, and it has shown remarkable efficacy in improving motor function and survival in clinical trials. While the initial data from

TABLE 1 Treatment options currently in use for spinal muscular atrophy.

Treatment	Nusinersen (Spinraza)	Onasemnogen abeparvovec (Zolgensma)	Risdiplam (Evrysdi)
Class	Antisense oligonucleotide	Adeno-associated virus (AAV) based gene therapy	Small molecule
Mechanism	Improves <i>SMN2</i> splicing to produce full-length SMN protein	Provides a functioning SMN trans gene	Improves <i>SMN2</i> splicing to produce full-length SMN protein
Administrative route	Intrathecal injection	Intravenous injection	Oral
FDA approved age categories	All	Greater than 2 years	More than two months
Frequency	Dosing schedule: 4 loading doses in the first 2 months, then every 4 months	Just one time dose (single dose)	Daily
Problems with current treatments	Unable to get a lumbar puncture done	AAV9 antibodies present at the baseline	Interactions between drugs
FDA approval	December 2016	May 2019	August 2020
Cost	\$125,000 per dosage (approx.)	\$2.125 million per treatment	\$100,000–\$340,000 annually
Unfavourable outcomes	Lumbar puncture problems, proteinuria, Thrombocytopenia	Transaminitis, thrombocytopenia, troponemia, and acute liver damage	Diarrhoea, rash, and fever

clinical trials and real-world experience have shown sustained benefits of Zolgensma treatment over several years, including improvements in motor function and survival, more long-term follow-up is needed to fully understand the duration of these benefits. Clinical trials and observational studies are ongoing to assess the durability of Zolgensma's effects, including its impact on motor function, respiratory function, quality of life, and survival rates over extended periods. These studies involve monitoring patients treated with Zolgensma for several years to track their progress and detect any potential changes in treatment outcomes over time. It's important to note that as research continues and more data become available, our understanding of the long-term benefits and potential limitations of Zolgensma treatment will continue to evolve. Patients and caregivers should work closely with healthcare providers to stay informed about the latest research findings and recommendations regarding the use of Zolgensma in the management of SMA (65, 72).

Risdiplam (Evrysdi™) was authorized by the FDA as of 7 August 2020, as the first oral medication for children as young as 2 months old and adults with SMA. It is a collaborative development effort involving Roche, PTC Therapeutics Inc., and the SMA Foundation, aimed at addressing spinal muscular atrophy (56, 73). Risdiplam serves as a modifier of mRNA splicing that leads to an elevation in SMN protein expression (74). It is a tiny molecule that changes the splicing of the SMN2 by binding to two locations in the SMN2 pre-mRNA. These sites are known as the 5' splice site (5' ss) of intron number 7 and the exon splicing enhancer 2 (ESE2) of exon 7 (75). Increases in full-length SMN mRNA and protein levels are caused by the unique specificity of binding two sites, which also reduces impact on other pre-mRNA splicing and prevents the likelihood of off-target effects (76). According to preclinical studies, risdiplam can reach the central nervous system and peripheral organs *in vivo* and can result in a significant increase of SMN protein in the blood, brain, and muscles, as well as an increase in survival in various SMA mouse models (77). While risdiplam's systemic distribution in preclinical tests with oral administration allowed for the possibility of an impact on other tissues, nusinersen's intrathecal delivery method mostly limited its effect to motoneurons of the central nervous system (78). Previous studies in human and murine models suggest that SMA may in fact be considered a multi-system disorder involving the neuromuscular junction, cardio-vascular system, lung, gastrointestinal-tract, and liver (79). Risdiplam has shown significant improvements in motor function and has the advantage of being an oral therapy, making it a more convenient option for many patients (80).

SMA treatments have evolved notably in recent years, particularly as previously stated gene therapies like Zolgensma and disease-modifying drugs like Spinraza (nusinersen). Much more significant perspective, which should consider insurance coverage, availability across regions, and efforts to improve access to SMA treatments. While these drugs offer a promising treatment option for children with SMA, they are highly costly, as seen in Table 1. According to studies, certain governments have made efforts to design policies for such disease treatments, such as: The Department of Revenue, Ministry of Finance, govt. of India had issued Notification No. 46/2021-Customs dated 30.09.2021, which waives all Basic Customs Duty (BCD) and Integrated Goods and Services Tax (IGST) on drugs imported (personal use only) for the treatment of spinal muscular atrophy (SMA) rare disease, making medicines for SMA rare disease more affordable (81). Government of India also made a provision for financial assistance of up to Rs. 50 lakhs to patients suffering from any

category of Rare Diseases such as SMA and for treatment at any of the Centres of Excellence (CoE) identified in the NPRD-2021, outside of the Rashtriya Arogya Nidhi umbrella scheme (82). The National Health Service (NHS) England, for example, states that Biogen (the pharmaceutical company that manufactures treatment for SMA) will make the treatment for spinal muscular atrophy (SMA) available to the youngest and most severely affected (SMA type 1) patients immediately, with NHS England offering funding contingent on the National Institute for Health and Care Excellence (NICE) publication of final guidance. In Singapore, the Rare Disease pay has been established to pay five drugs to treat three rare diseases. In Malaysia and Australia, qualifying patients are given discounted access to pricey and life-saving medications (83).

7 Rehabilitation (care and therapies) and disease management for spinal muscular atrophy

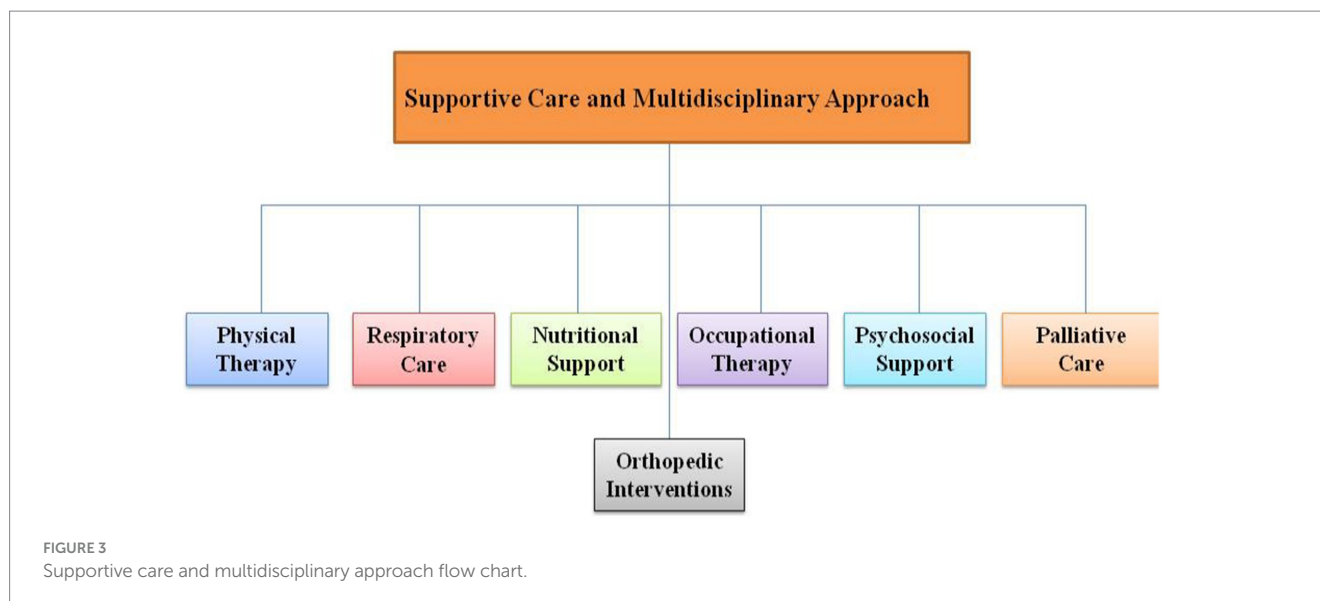
In addition to disease-modifying treatments, SMA management often involves a multidisciplinary approach as shown in Figure 3 that focuses on addressing the symptoms and complications associated with the disease. Supportive care strategies aim to improve the quality of life for individuals with SMA and include:

7.1 Physical therapy

Physical therapy is essential in managing muscle weakness, contractures, and maintaining range of motion (84, 85). People affected by spinal muscular atrophy may experience limitations in their ability to fully articulate their joints due to muscle weakness. This can potentially lead to the development of contractures, characterized by muscle tightness that may become permanent and restrict mobility (86). Physical therapy often incorporates exercises and stretching routines designed to enhance flexibility and overall functionality (87). These interventions aim to minimize the likelihood of joint contractures, mitigate the progression of scoliosis, and promote the maintenance of a healthy weight. Mounting evidence suggests that consistent participation in physical therapy sessions can yield positive outcomes in terms of both function and the progression of spinal muscular atrophy in patients (86, 87).

7.2 Respiratory care

The management of the respiratory system plays a pivotal role in addressing spinal muscular atrophy (88). Weakness in the chest muscles can hinder one's capacity to breathe or cough effectively, consequently elevating the likelihood of infections (89, 90). The available respiratory care solutions encompass both non-invasive and invasive methods: (i) non-invasive respiratory care comprise strategies that aim to circumvent or postpone the necessity for invasive procedures (88). Specialized apparatus, such as a ventilator or a bilevel positive airway pressure (BiPAP) machine, can provide a constant airflow to the lungs using a mask that covers the mouth and/or nose. Additionally, a home-based cough assist device may be utilized to facilitate coughing and the clearance of secretions. (ii) Invasive respiratory care establishes a protected passage to the lungs using an endotracheal tube inserted either



through the mouth (intubation) or directly into the trachea via a minor neck incision (tracheotomy) (91, 92).

7.3 Nutritional support

The weakening of muscles can result in some individuals with SMA experiencing a decline in their ability to chew and swallow proficiently. This situation increases the risk of food or liquids being aspirated into the lungs, potentially leading to respiratory infections (93, 94). To address this, a temporary or permanent feeding tube may be inserted to ensure the essential intake of nutrition and hydration (93). Broadly speaking, there are two categories of feeding tubes: those inserted through the nose and those placed in the abdominal area. Nasogastric (NG) tubes are inserted through the nasal passage and deliver nutrition directly into the stomach (95, 96). These are typically employed for patients requiring short-term feeding tube access and are conveniently replaceable (95). Gastrostomy (G) tubes are surgically implanted through the abdominal wall and directly into the stomach (97–99). Due to their ease of maintenance, they are often the favored choice for individuals in need of extended-term feeding assistance.

7.4 Orthopedic interventions

Orthopedic surgery may be required in cases where there are severe joint contractures or scoliosis (98, 100). Scoliosis, characterized by a spinal curvature, can be a challenge for individuals with spinal muscular atrophy as a consequence of muscle weakness (101). An orthopedic specialist may propose postural support in the form of bracing or recommend surgical intervention to address scoliosis (98, 101).

7.5 Occupational therapy

Occupational therapists work with SMA patients to enhance their ability to perform daily tasks and improve their independence (102,

103). They assess patients' needs and recommend assistive devices or home modifications to facilitate daily activities. Their role includes: adaptive techniques means teaching individuals adaptive techniques and recommending assistive devices that enable greater independence (104). Home modifications means assessing home environments and suggesting modifications to make daily tasks more manageable (105). Assisting with communication means in cases of severe SMA, occupational therapists can help individuals use communication devices to facilitate interaction with others (106).

7.6 Psychosocial support

SMA affects not only the physical health but also the emotional and psychosocial well-being of patients and their families (107). Ensuring the holistic care of a patient with SMA and their family is insufficient without the monitoring and treatment of their psychosocial welfare. Requirements differ based on the patient's age and specific sub-types of SMA. Psychosocial health can be influenced by various elements, including social and emotional factors as well as treatment factors such as innovative therapies. Psychosocial care should encompass a wide range of characteristics, including social and cognitive development, quality of life, and the impact on patient and family functioning in various situations such as home, school, or job. The care of SMA should include the involvement of a mental health practitioner, such as a psychologist, psychiatrist, or neuropsychologist, as well as a social worker who has specialised experience in assisting patients with chronic diseases. Assessments should be considered around the time of diagnosis, before entering school, and after a change in functionality. Implementing psychologically informed care and employing a range of interventions has the potential to mitigate psychological morbidity in both children and parents. During every multidisciplinary appointment, it is important to assess the individual's mental health and quality of life. If deemed essential, the mental health clinician will be involved in evaluating the psychological state of the patient, as well as their parents and siblings (107). Psychosocial support addresses these aspects and may include: (i) counseling;

individual and family counseling can help individuals and caregivers cope with the emotional challenges of living with SMA (107, 108). (ii) Support groups: joining support groups, either in person or online, can provide a sense of community and shared experiences. (iii) Mental health services: access to mental health services is essential for addressing anxiety, depression, and stress that may result from the condition (108, 109).

7.7 Palliative care

For individuals with advanced SMA or those with severe complications, palliative care can provide symptom management, pain relief, and emotional support to enhance quality of life (110).

7.8 Disease management approaches for SMA management

7.8.1 Supportive care and multidisciplinary approach

The management of SMA requires a multidisciplinary team approach involving various healthcare professionals to address the diverse needs of individuals with the condition. The team may include neurologists, physical and occupational therapists, respiratory therapists, nutritionists, orthopedic surgeons, and social workers. This collaborative approach ensures that the physical, emotional, and psychosocial aspects of SMA are managed comprehensively (111). Supportive care is the fundamental aspect of clinical management in spinal muscular atrophy (SMA). The development of disease-modifying medications such as nusinersen, onasemnogene abeparvovecxioi, and risdiplam has provided improved treatment choices for the most severe forms of the condition. These medications have increased survival rates and brought hope for a longer and better quality of life. Additionally, they have influenced the way healthcare is provided for these patients. Although there have been some improvements in the field, adults living with SMA and those transitioning into adulthood have been somewhat overlooked, despite the emergence of studies and advancements such as enhanced respiratory care, home adaptations, and devices that promote greater independence, like power wheelchairs and voice amplifiers. It is important for everyone to acknowledge and appreciate these achievements. The effects of fragmented care might be intensified for individuals migrating from paediatric to adult care, as they no longer receive the same degree of coordinated assistance provided in paediatric settings. According to reports, individuals who are transferring from paediatric to adult healthcare services face challenges in understanding and interacting with a complex health system and new specialists. They commonly describe this experience as “challenging and intimidating.”

In addition, adults with SMA may have difficulties during this phase of transition, particularly when they need to relocate (e.g., for higher education), as this necessitates them to become part of a new healthcare system. Although not prevalent within the SMA community as a whole, certain jurisdictions have acknowledged this issue and have adopted targeted measures to mitigate its effects. For instance, they have established transitional clinics where medical professionals from both adult and paediatric fields participate in appointments. We advocate for increased implementation of optimal methods and specialised procedures (such as established transitional

care clinics, communication paths between paediatric and adult experts, and a nationwide network of specialists) that streamline the transition to adult care and the transfer of knowledge (46).

7.8.2 Assistive devices and technology

The use of assistive devices and technology plays a significant role in SMA management. These devices help individuals with SMA lead more independent and fulfilling lives (112). Examples include: wheelchairs, scooters, and other mobility aids provide individuals with the freedom to move and explore their environments (113). Augmentative and alternative communication (AAC) devices assist those with severe SMA in expressing themselves (106). These systems enable individuals to control various aspects of their environment, such as lights, doors, and appliances, through adapted technology. Adapting the home environment with features like ramps, wider doorways, and accessible bathrooms enhances accessibility (105). Adaptive technology and software allow individuals with limited physical mobility to use computers and access the internet (104).

8 Emerging therapies

Research into SMA continues, with several promising therapies under investigation. These therapies include small molecule drugs, gene-editing technologies, and exon-skipping therapies, among others. The goal is to further enhance the disease-modifying potential and offer a more comprehensive treatment approach for SMA. Advances in genetic testing have made it easier to diagnose SMA accurately and offer prenatal testing for at-risk pregnancies. These advancements include: NGS has become a powerful tool in identifying rare or atypical mutations in the *SMN1* gene and other related genes. It can uncover genetic variations that were previously challenging to detect (114, 115). Techniques like chorionic villus sampling and amniocentesis allow for the diagnosis of SMA in the fetus, enabling informed reproductive decisions and early intervention if the fetus is affected (116, 117).

8.1 Gene-editing technologies

Emerging gene-editing techniques, such as CRISPR-Cas9, offer the potential to correct genetic mutations directly, providing a curative approach to SMA. These technologies are in the early stages of development and are being explored in preclinical studies. In addition to this, CRISPR technology, which expands the scope of genetic engineering and gene treatments, enables the treatment of a wide range of hereditary illnesses. Some prior research in the literature show that SMA can be treated using the CRISPR method. Homology directed repair (HDR)-based CRISPR technology, which produces a high rate of in-del (insertion-deletion) mutations rather than editing, has been proven unsuitable for therapeutic purposes. CRISPR-prime editing (PE) technology is a novel type of gene editing technique that enables precise genomic alterations without the need for double-strand breaks or donor DNA sequences. The CRISPR-prime editing approach has also been employed in rare disorders like as sickle cell anaemia and Tay–Sachs, and its effectiveness in editing diverse harmful variants has been proven. However, CRISPR Prime Editing-mediated gene editing for spinal muscular atrophy (SMA) has yet to be investigated (114).

8.2 Small molecule therapies

Small molecules that target specific pathways involved in SMA are also under investigation. These drugs aim to increase SMN protein production and improve motor function (116).

8.3 Combination therapies

Researchers are exploring the use of combination therapies, including a mix of SMN2-targeting drugs and other treatments, to enhance the efficacy of SMA management (118). Combining different therapeutic strategies to maximise SMA treatment outcomes is an exciting approach. Limited data supports the efficacy of expensive drug combinations in people, encouraging clinicians and scientists to examine all therapeutic options (56, 119). A combination of SMN-dependent ASO-inducing SMN2 exon inclusion and SMN-independent myostatin inhibition yielded positive results in a SMA animal model (56, 120). A limited sample of patients were treated with a combination of Zolgensma and nusinersen, but the long-term benefits remain unclear. Zolgensma and nusinersen have distinct modes of action, making drug-to-drug interactions less common. Nusinersen targets an intron sequence to increase exon 7 inclusion. The transplanted Zolgensma gene lacks introns and hence should not interfere with nusinersen translation. Zolgensma treatment should be approached with caution due to the reported adverse event of thrombocytopenia associated with nusinersen. Long-term follow-up data, particularly in pre-symptomatic patients, is needed to evaluate the effectiveness and hazards of combination therapy (56). Combination therapies, treatments and advocacy initiatives have played an important role in determining research orientations and legislative changes in the management of spinal muscular atrophy (SMA). Advocacy groups such as cure SMA, SMA foundation, and fight SMA have been instrumental in catalyzing SMA research. By raising awareness, funding research initiatives, and fostering collaborations among scientists, these organizations have accelerated the pace of discovery in understanding the underlying genetic mechanisms of SMA, identifying potential therapeutic targets, and developing innovative treatment strategies.

8.4 Early intervention and pre-symptomatic treatment

Research has shown the benefits of early intervention, even before the onset of symptoms, in infants with SMA (121). The nurture study demonstrated that early treatment with nusinersen in pre-symptomatic infants significantly improved motor function and developmental outcomes (122).

8.5 Patient and caregiver advocacy

SMA patient and caregiver advocacy groups have played a crucial role in raising awareness, driving research, and improving access to care and treatments. Their efforts have been instrumental in advancing the SMA field (123).

9 Conclusion

Thirty years after the discovery of the SMN gene, global scientific efforts have successfully transformed spinal muscular atrophy (SMA) into a manageable condition. Three distinct drugs utilizing cutting-edge technology—gene therapy, antisense oligonucleotides (ASOs), and small molecules focused on SMN2 splice correction—have gained approval from both the FDA and EMA, demonstrating remarkable enhancements, particularly when administered prior to the onset of symptoms. SMA, known for its substantial economic impact, has become even more financially demanding with the introduction of these novel therapies. Addressing the considerable economic burden associated with these treatments has led to an increasing advocacy for the inclusion of SMA in newborn screening (NBS) programs. While the existing therapies are likely sufficient for immediate administration after birth in cases of intermediate and mild SMA, questions arise regarding whether individuals with only two SMN2 copies will follow a trajectory similar to their age-matched counterparts and if they may require additional SMN-independent therapies. Comprehensive longitudinal studies are imperative to explore potential new phenotypes linked to these innovative therapies. Despite the presence of biomarkers associated with disease progression, further investigations are needed to identify potential non responders, enabling them to transition to alternative therapies. SMA treatments are often expensive, prompting concerns regarding equal access for all patients, especially in low-income areas or nations with limited healthcare resources. Addressing pricing and guaranteeing access to these life-changing medications for all SMA patients worldwide remains a serious concern. Numerous unanswered questions persist, necessitating meticulous future research. Nonetheless, SMA stands as a model illustrating how genetic insights can pave the way for the development of targeted therapies.

Author contributions

PB: Formal analysis, Data curation, Writing – original draft. SS: Writing – review & editing, Supervision, Writing – original draft. GR: Writing – review & editing, Supervision. SK: Writing – original draft, Visualization. AS: Writing – review & editing, Supervision, Formal analysis.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Development of a predictive model for 1-year postoperative recovery in patients with lumbar disk herniation based on deep learning and machine learning

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Background: The aim of this study is to develop a predictive model utilizing deep learning and machine learning techniques that will inform clinical decision-making by predicting the 1-year postoperative recovery of patients with lumbar disk herniation.

Methods: The clinical data of 470 inpatients who underwent tubular microdiscectomy (TMD) between January 2018 and January 2021 were retrospectively analyzed as variables. The dataset was randomly divided into a training set ($n = 329$) and a test set ($n = 141$) using a 10-fold cross-validation technique. Various deep learning and machine learning algorithms including Random Forests, Extreme Gradient Boosting, Support Vector Machines, Extra Trees, K-Nearest Neighbors, Logistic Regression, Light Gradient Boosting Machine, and MLP (Artificial Neural Networks) were employed to develop predictive models for the recovery of patients with lumbar disk herniation 1 year after surgery. The cure rate score of lumbar JOA score 1 year after TMD was used as an outcome indicator. The primary evaluation metric was the area under the receiver operating characteristic curve (AUC), with additional measures including decision curve analysis (DCA), accuracy, sensitivity, specificity, and others.

Results: The heat map of the correlation matrix revealed low inter-feature correlation. The predictive model employing both machine learning and deep learning algorithms was constructed using 15 variables after feature engineering. Among the eight algorithms utilized, the MLP algorithm demonstrated the best performance.

Conclusion: Our study findings demonstrate that the MLP algorithm provides superior predictive performance for the recovery of patients with lumbar disk herniation 1 year after surgery.

KEYWORDS

predictive model, machine learning, deep learning, lumbar disk herniation, lumbar JOA score

Introduction

Lumbar disk herniation (LDH) is a common and frequently occurring disease that is the most common cause of back and leg pain, resulting in great suffering such as reduced ability to work and learn, reduced quality of life, and even disability (1). Surgery, especially tubular microscopic discectomy (TMD), has become the conventional treatment for LDH in recent years (2). TMD is a minimally invasive method to remove the herniated disk from the posterior approach using surgical microscopic instruments. However, there are several factors that can affect postoperative recovery (3). Clinical predictive modeling (CPM) is a statistical model based on multiple pathologies of the disease that can predict the risk of certain future outcomes in patients with certain characteristics (4, 5). Building statistical models requires a large amount of clinical data, and machine learning (ML) algorithms can accurately process the raw data, analyze the connections between important data, and make accurate decisions (6). With the widespread use of machine learning, deep learning, as an important branch of machine learning, has advantages in automatic feature learning and function simulation construction (7–9). Due to the complexity and size of clinical data, using deep learning models and machine learning can improve the accuracy of models and predictions in data processing, as well as in building clinical models (10, 11). The goal of this study is to develop a predictive model based on deep learning and machine learning for the recovery of patients with lumbar disk herniation 1 year after surgery.

Methods

All data for this study were obtained from the Department of Neurosurgery, Fujian Medical University Union Hospital. The study recorded the medical variables of patients who were hospitalized and underwent TMD between January 2016 and January 2018. The data included patients' basic information, medical history, physical examination, preoperative test results, and preoperative scores. Retrospective analysis was conducted, and deep learning and machine learning algorithms were used to establish a predictive model for the 1-year postoperative recovery of patients with lumbar disk herniation.

Inclusion criteria

(1) Age of inclusion: 12–85 years old; (2) The prominent lumbar segments are: L3/4, L4/5, or L5/S1, including cases of combined protrusions involving two or three segments. (3) have typical sciatica with or without lumbar pain and other symptoms; (4) those who have been ineffective after standardized conservative treatment for more than 3 months and seriously affect their lives, or those with severe pain, cauda equina dysfunction, muscle strength loss, muscle atrophy, and other symptoms; (5) the straight leg raising test on the affected side is less than or equal to 70°; (6) confirmed by CT and MRI lumbar disk protrusion, and the location of the protrusion matches the corresponding neurological symptoms; and (7) receiving standardized unilateral paraspinal tubular microdiscectomy (TMD) technology treatment and a consistent physical therapy regimen (12, 13).

For more information about this study and the standardized surgical procedures at our institution, please refer to our previously published study (14).

Exclusion criteria

(1) Those with missing imaging data or unable to follow up as required; (2) those with segmental lumbar instability suggested by frontal and lateral lumbar X-ray and hyperextension and hyperflexion; (3) those with other serious physical, psychological, or mental diseases; (4) those with rheumatic immune diseases that may cause similar symptoms; and (5) those who are participating in other clinical trials.

Data collection

To construct and validate the prognostic model, we retrospectively collected clinical data related to patients with LDH who met the inclusion and exclusion criteria. The potential predictors included 42 variables related to patients' medical history, examination, and preoperative test results, with the cure rate of the lumbar Japanese Orthopedic Association (JOA) score 1 year after TMD as the outcome measure.

The following variables were included as factors in the analysis: age, gender, height, weight, body mass index (BMI), high-risk occupation (occupations that require prolonged sedentary or high-intensity physical activity), family history (with first-degree relatives affected by LDH), history of lumbar trauma, duration of disease, duration of preoperative conservative treatment, duration of preoperative pain medication, low back pain, underlying diseases (hypertension, diabetes), history of smoking, history of alcohol abuse, angle of preoperative physical examination (as measured by the straight leg raise test), sensory impairment, muscle strength classification of the affected limb, Barthel scale, serum creatine kinase (CK), and lumbar degeneration, associated lumbar disk herniation, American Society of Anesthesiologists (ASA) grading, Oswestry Disability Index (ODI) score, preoperative low back pain and leg pain numerical rating scale (NRS) scores, the number of surgical segments as determined by the JOA, surgical time, and intraoperative bleeding. These are shown in Table 1. The cure rate score of the lumbar JOA 1 year after TMD surgery was also used as an outcome measure. Further details on these factors are provided in Supplementary material 1.

Outcome indicators

Cure rate scores for lumbar JOA score at 1 year after TMD surgery were calculated using the same method as before the operation. The cure rate was calculated as follows:

$$\left[\frac{(\text{post treatment score} - \text{pre treatment score})}{(\text{full score } 29 - \text{pre treatment score})} \times 100\% \right]$$

This rate reflects the improvement of lumbar spine function before and after treatment, and is utilized to evaluate the clinical efficacy of the intervention. A cure rate of 100% indicates complete recovery, while a cure rate of greater than 60% is considered to be significantly effective. Improvement rates falling within the range of 25–60% are categorized as effective, while

TABLE 1 Descriptive statistics of different influencing factors in a study population grouped by whether the improvement in lumbar JOA score was >60% 1 year after TMD.

Variables	Total (470)	JOA ≤ 60% (271)	JOA > 60% (199)	p-value
Age	51.81 ± 14.36	54.31 ± 14.02	48.40 ± 14.14	<0.001
Preop_JOA	13.11 ± 3.43	12.75 ± 3.09	13.59 ± 3.80	<0.001
Preop_ODI	48.29 ± 20.24	50.66 ± 19.00	45.05 ± 21.43	<0.001
Intraop bleeding	22.73 ± 13.56	24.23 ± 15.84	20.68 ± 9.28	<0.001
Surgery time	2.89 ± 0.75	2.99 ± 0.72	2.76 ± 0.77	<0.001
SD	1.37 ± 0.19	1.38 ± 0.16	1.35 ± 0.22	0.2883
Gender				0.5189
Female	208(44.26)	116(42.80)	92(46.23)	
Male	262(55.74)	155(57.20)	107(53.77)	
Height				<0.001
<40	102(21.70)	68(25.09)	34(17.09)	
40 ~ <60	159(33.83)	72(26.57)	87(43.72)	
≥60	209(44.47)	131(48.34)	78(39.20)	
Weight				0.1359
<50	39(8.30)	23(8.49)	16(8.04)	
<60	131(27.87)	62(22.88)	69(34.67)	
<70	180(38.30)	113(41.70)	67(33.67)	
<80	82(17.45)	49(18.08)	33(16.58)	
<90	26(5.53)	16(5.90)	10(5.03)	
≥90	12(2.55)	8(2.95)	4(2.01)	
BMI				<0.001
<18.5	7(1.49)	3(1.11)	4(2.01)	
<24	193(41.06)	90(33.21)	103(51.76)	
<28	228(48.51)	153(56.46)	75(37.69)	
≥28	42(8.94)	25(9.23)	17(8.54)	
History of lower back trauma				1.0000
No	452(96.17)	261(96.31)	191(95.98)	
Yes	18(3.83)	10(3.69)	8(4.02)	
Hypertension				0.1546
No	374(79.57)	209(77.12)	165(82.91)	
Yes	96(20.43)	62(22.88)	34(17.09)	
Diabetes				0.0838
No	428(91.06)	241(88.93)	187(93.97)	
Yes	42(8.94)	30(11.07)	12(6.03)	
Alcohol use				<0.001
No	406(86.38)	221(81.55)	185(92.96)	
Yes	64(13.62)	50(18.45)	14(7.04)	
Smoking				0.3361
No	361(76.81)	213(78.60)	148(74.37)	
Yes	109(23.19)	58(21.40)	51(25.63)	

(Continued)

TABLE 1 (Continued)

Variables	Total (470)	JOA ≤ 60% (271)	JOA > 60% (199)	p-value
ASA				0.3566
1	305(64.68)	171(62.73)	134(67.34)	
2	152(32.34)	90(33.21)	62(31.16)	
3	13(2.77)	10(3.69)	3(1.51)	
Family history				0.2410
No	419(89.15)	246(90.77)	173(86.93)	
Yes	51(10.85)	25(9.23)	26(13.07)	
Preop_Painkiller				0.0014
No	295(62.77)	153(56.46)	142(71.36)	
Yes	175(37.23)	118(43.54)	57(28.64)	
Preop_Hormone				0.4476
No	438(93.19)	250(92.25)	188(94.47)	
Yes	32(6.81)	21(7.75)	11(5.53)	
CTT				0.1501
≤6	290(61.70)	162(59.77)	104(64.32)	
≤12	43(9.15)	22(8.12)	21(10.55)	
≤24	75(15.96)	53(19.56)	22(11.06)	
>24	62(13.19)	34(12.55)	28(14.07)	
WLPT				0.0053
≤6	201(42.98)	112(41.32)	89(45.23)	
≤12	76(15.96)	43(15.87)	33(16.08)	
≤24	43(9.15)	15(5.54)	28(14.07)	
>24	150(31.91)	101(37.27)	49(24.62)	
Lumbago				0.0587
No	113(24.04)	56(20.66)	57(28.64)	
Yes	357(75.96)	215(79.34)	142(71.36)	
SLETA				0.6709
<40	157(33.40)	93(34.32)	64(32.16)	
40~<60	202(42.98)	118(43.54)	84(42.21)	
≥60	111(23.62)	60(22.14)	51(25.63)	
DOS				0.2122
Nothing	307(65.32)	181(66.79)	126(63.32)	
Mild	137(29.15)	72(26.57)	65(32.66)	
Obvious	26(5.53)	18(6.64)	8(4.02)	
MS				0.4210
1	2(0.43)	2(0.74)	0	
2	1(0.21)	1(0.37)	0	
3	5(1.06)	4(1.48)	1(0.50)	
4	91(19.15)	54(19.93)	37(18.09)	
5	371(78.94)	210(77.49)	161(80.90)	
Babinski				0.9225
Negative	459(97.66)	264(97.42)	195(97.99)	

(Continued)

TABLE 1 (Continued)

Variables	Total (470)	JOA ≤ 60% (271)	JOA > 60% (199)	p-value
Positive	11(2.34)	7(2.58)	4(2.01)	
CK				0.4958
≤198	431(91.70)	246(90.77)	185(92.96)	
>198	39(8.30)	25(9.23)	14(7.04)	
Number				<0.001
1	129(27.45)	44(16.24)	85(42.71)	
2	292(62.13)	199(73.43)	93(46.73)	
3	29(6.17)	14(5.17)	15(7.54)	
4	16(3.40)	12(4.43)	4(2.01)	
5	4(0.85)	2(0.74)	2(1.01)	
SSN				0.2220
1	460(97.87)	263(97.05)	197(98.99)	
2	8(1.70)	7(2.58)	1(0.50)	
3	2(0.43)	1(0.37)	1(0.50)	
Protrusion direction				<0.001
Left	346(73.62)	224(82.66)	122(61.31)	
Right	124(26.38)	47(17.34)	77(38.69)	
Collapse				0.7114
No	392(83.40)	228(84.13)	164(82.41)	
Yes	78(16.60)	43(15.87)	35(17.59)	
LS				1.0000
No	450(95.74)	259(95.57)	191(95.98)	
Yes	20(4.26)	12(4.43)	8(4.02)	
Osteoporosis				0.0284
No	424(90.21)	237(87.45)	187(93.97)	
Yes	46(9.79)	34(12.55)	12(6.03)	
Calcification				<0.001
No	126(26.81)	44(16.24)	82(41.21)	
Yes	344(73.19)	227(83.76)	117(58.79)	
Sagittal_Disc_ Herniation_ Pos				0.0053
−3	3(0.64)	0	3(1.51)	
−2	21(4.47)	8(2.95)	13(6.53)	
−1	313(66.60)	198(73.06)	115(57.79)	
0	117(24.89)	59(21.77)	58(29.15)	
1	13(2.77)	5(1.85)	8(4.02)	
2	3(0.64)	1(0.37)	2(1.01)	
Location				<0.001
1	117(24.89)	52(19.19)	65(32.66)	
2	305(64.89)	201(74.17)	104(52.26)	
3	44(9.36)	17(6.27)	27(13.57)	
4	4(0.85)	1(0.37)	3(1.51)	

(Continued)

TABLE 1 (Continued)

Variables	Total (470)	JOA ≤ 60% (271)	JOA > 60% (199)	p-value
Grade				<0.001
1	101(21.49)	41(15.13)	60(30.15)	
2	309(65.74)	201(74.17)	108(54.27)	
3	60(12.77)	29(10.70)	31(15.58)	
Modic change				<0.001
0	105(22.34)	39(14.39)	66(33.17)	
1	244(51.91)	176(64.94)	68(34.17)	
2	55(11.70)	26(9.59)	29(14.57)	
3	66(14.04)	30(11.07)	36(18.09)	
Pfirrmann				<0.001
1	2(0.43)	0	2(1.01)	
2	29(6.17)	10(3.69)	19(9.55)	
3	102(21.70)	32(11.81)	70(35.18)	
4	286(60.85)	191(70.48)	95(47.74)	
5	51(10.85)	38(14.02)	13(6.53)	
Lumbago_ NRS				<0.001
0–2	104(22.13)	35(12.92)	69(34.67)	
3–4	241(51.28)	166(61.25)	75(37.69)	
5–6	90(19.15)	52(19.19)	38(19.10)	
7–8	35(7.45)	18(6.64)	17(8.54)	
Leg_Pain_ NRS				<0.001
0–2	19(4.04)	9(3.32)	10(5.03)	
3–4	116(24.68)	47(17.34)	69(34.67)	
5–6	291(61.91)	193(71.22)	98(49.25)	
7–8	44(9.36)	22(8.12)	22(11.06)	
High risk occupation				<0.001
No	148(31.49)	47(17.34)	101(50.75)	
Yes	322(68.51)	224(82.66)	98(49.25)	
Numbness after				0.4124
No	315(67.02)	177(65.31)	138(69.35)	
Yes	155(32.98)	94(34.69)	61(30.65)	
Reduction of lumbago				<0.001
No	339(72.13)	148(54.61)	191(95.98)	
Yes	131(27.87)	123(45.39)	8(4.02)	
Reduction of leg				<0.001
No	349(74.26)	151(55.72)	198(99.50)	
Yes	121(25.74)	120(44.28)	1(0.50)	
JOA improvement				<0.001

(Continued)

TABLE 1 (Continued)

Variables	Total (470)	JOA ≤ 60% (271)	JOA > 60% (199)	p-value
No	25(5.32)	25(9.23)	0	
Yes	445(94.68)	246(90.77)	199(100.00)	
ODI difference				<0.001
No	81(17.23)	66(24.35)	15(7.54)	
Yes	389(82.77)	205(75.65)	184(92.46)	
Reoperation				0.0012
No	454(96.60)	255(94.10)	199(100.00)	
Yes	16(3.40)	16(5.90)	0	
Recurrence				<0.001
No	442(94.04)	243(89.67)	199(100.00)	
Yes	28(5.96)	28(10.33)	0	

CTT, Conservative treatment time; WLPT, Waist leg pain time, SLETA, Straight leg elevation test angle of affected limb, DOS, Disturbance of sensation; MS, Muscle strength; Number, Number of salient segments; SSN, Surgical segment number; Segment, Number of operative segments; Collapsa, Collapse of intervertebral space; LS, Lumbar spondylolisthesis; Calcification, Calcification of ligaments hyperplasia of bone; SD, Sagittal diameter; Position, Sagittal disk herniation horizontal position; Location, Transected herniated disk location; Grade, Grading of transected disk herniation; Numbness after, Numbness in the year after surgery; Reduction of lumbago, Reduction of lumbago NRS 1 year after surgery ≥ 2 ; Reduction of leg, Reduction of leg pain NRS 1 year after surgery > 2 ; JOA improvement, JOA improvement rate 1 year after surgery ≥ 25 ; ODI difference, ODI difference 1 year after surgery > 20 ; Proximal lumbar process, Proximal lumbar process within 1 year after surgery; Recurrence, Recurrence occurred within 1 year after surgery.

those below 25% are classified as ineffective. To process the data, patients with an improvement rate of lumbar JOA score $> 60\%$ (significant efficacy or cure) 1 year after TMD were recorded as 1, while patients with an improvement rate of lumbar JOA score $\leq 60\%$ (effective but not significant or ineffective) were recorded as 0.

Feature engineering

Feature engineering is a process that involves transforming raw data into features that are more suitable for modeling. By doing so, the resulting features are able to capture relevant patterns, thereby improving the predictive accuracy of machine learning and deep learning models on unseen data (15).

In this study, the feature engineering process began by transforming raw data into more suitable features for modeling through data preprocessing and feature selection. Missing values were addressed using mean interpolation (16, 17), and the data were standardized using Z-score normalization to ensure uniformity, with all features having a mean of 0 and a standard deviation of 1. Further, before applying the features to eight different predictive algorithms, feature selection was carried out using the Mann–Whitney U test, retaining only those features with *p* values less than 0.05. To reduce redundancy, a Spearman correlation matrix heatmap was used to identify highly correlated features ($|p| > 0.9$), which were eliminated, except for one retained to maintain descriptive power. The final selection utilized LASSO regression with 10-fold cross-validation to identify features with non-zero coefficients essential for modeling.

Spearman ρ correlation matrix heat map

We conducted a correlation analysis of the data using a Spearman ρ correlation matrix heat map (18). The Spearman correlation matrix heat map is suitable for analyzing data that do not conform to a normal distribution, as well as data that contain categorical variables. It can measure the correlation between any two variables, with a value of +1 indicating a total positive correlation, -1 indicating a total negative correlation, and 0 indicating no correlation. The results of the correlation analysis can be visually represented using a heat map, which uses color to indicate the magnitude of the correlation, making it easier and more intuitive to interpret the results.

Machine learning and deep learning

We employed a systematic framework based on machine learning and deep learning to construct prognostic models. To this end, we divided the data into a training dataset for developing the predictive model and a test dataset for evaluating the accuracy of the model (19). The data were randomly divided into two groups in a ratio of 70:30, with 70% ($n = 329$) of the samples designated as the training set for developing the predictive model, and 30% ($n = 141$) of the samples designated as the test set for evaluating the accuracy of the model. Once the training set was defined, an optimal model was developed using eight different machine learning algorithms, including Random Forests, Extreme Gradient Boosting, Support Vector Machines, Extra Trees, K-Nearest Neighbors, Logistic Regression, Light Gradient Boosting Machine, and MLP (Artificial Neural Networks) from scikit-learning (version: 0.18) in python.

To optimize the accuracy of the predictive models, a grid search was conducted on the hyperparameters for each of the eight ML algorithms used. A 10-fold cross-validation was employed, whereby the training data set was divided into 10 equally-sized folds, and the model was created using 90% of the data in each fold, with the remaining data used to evaluate the model's accuracy. The process was repeated 10 times, with each fold being used for one of the 10 training steps (20, 21). The area under the receiver operating characteristic (ROC) curve, also known as area under the curve (AUC), was used as the primary accuracy metric during the grid search (22). The AUC is a performance measure that evaluates the strengths and weaknesses of the learner and is widely used in clinical settings to assess the performance of ML algorithms on test datasets (23). In addition to the AUC, Accuracy, AUC, Sensitivity, Specificity, PPV, NPV, Precision, Recall, and F1 values were also reported to provide a comprehensive picture of the algorithm's performance (22).

The modeling and prediction process for deep learning is similar to traditional machine learning, with the main difference being that deep learning is end-to-end and can automatically extract high-level features, greatly reducing the reliance on feature engineering in traditional machine learning (7).

Statistical analysis

Continuous variables were presented as mean $\pm$ standard deviation, while categorical variables were presented as frequencies and percentages. Group comparisons for categorical variables were conducted using the chi-square test or Fisher's exact test, whereas

differences between groups for quantitative variables were assessed using the *t*-test or Mann–Whitney U test. Statistical analyses were conducted at a significance level of 0.05 (two-tailed) using Python (version 3.9, <http://www.python.org>). A two-sided *p* value <0.05 was deemed statistically significant.

Results

General

A total of 470 patients meeting the inclusion and exclusion criteria were enrolled in this study. All patients underwent TMD surgery between January 2018 and January 2021 and were followed up for 1 year. In order to develop predictive models, 42 variables were collected, including gender, age, BMI, medical history, and preoperative indicators.

Correlation matrix heat map

Figure 1 presents the Spearman ρ correlation matrix heatmap, which is utilized to construct the model's independent variables. This

heatmap reveals that there is a medium to strong correlation between several pairs of variables: weight and gender $\rho=0.507$, BMI and weight $\rho=0.662$, Lumbago-NRS and Lumbago $\rho=0.474$, Preop_JOA and leg_pain_NRS $\rho=-0.439$, and Preop_JOA and Preop_ODI $\rho=-0.633$. The absolute strength of all other correlations did not exceed 0.40 ($|\rho| \leq 0.40$).

Machine learning and deep learning

After performing data preprocessing and segmenting the dataset into training and test sets, this study employed eight algorithms to develop the predictive model. Finally, 15 variables after Feature Engineering (Figure 2C) were used to input DL and ML algorithm, including high-risk occupation, preop_ODI, calcification, and other 12 variables. Each algorithm was also subjected to a hyperparameter grid search based on a 10-fold cross-validation and after finding the optimal hyperparameters, the models were used to generate predictions.

As shown in Figure 2 and Table 2, MLP exhibits the highest AUC values (Train AUC=0.872; Test AUC=0.840), also demonstrating superior performance across other metrics such as an Accuracy of

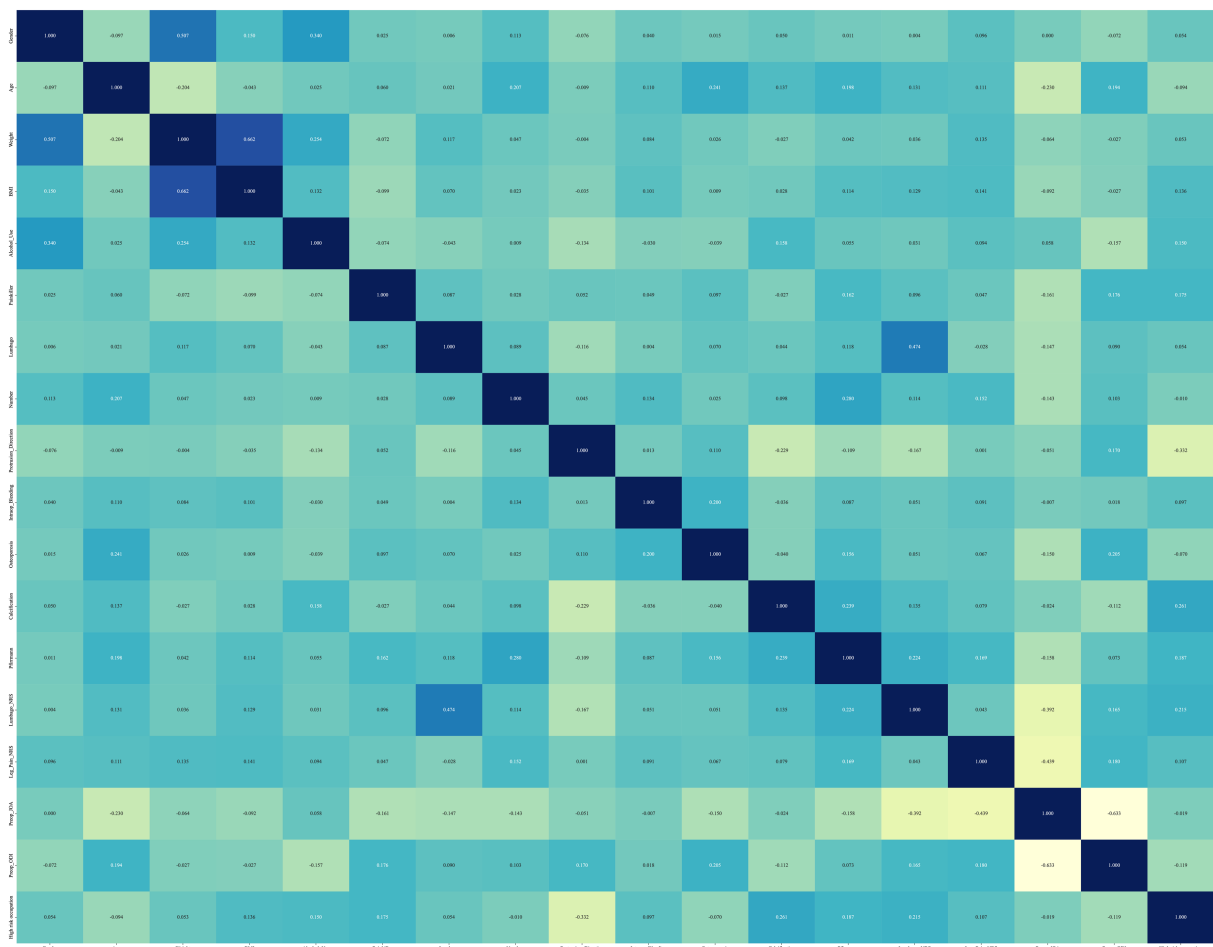


FIGURE 1 The Spearman ρ correlation matrix heat map used to construct the model independent variables. A large number of highly correlated features are eliminated.

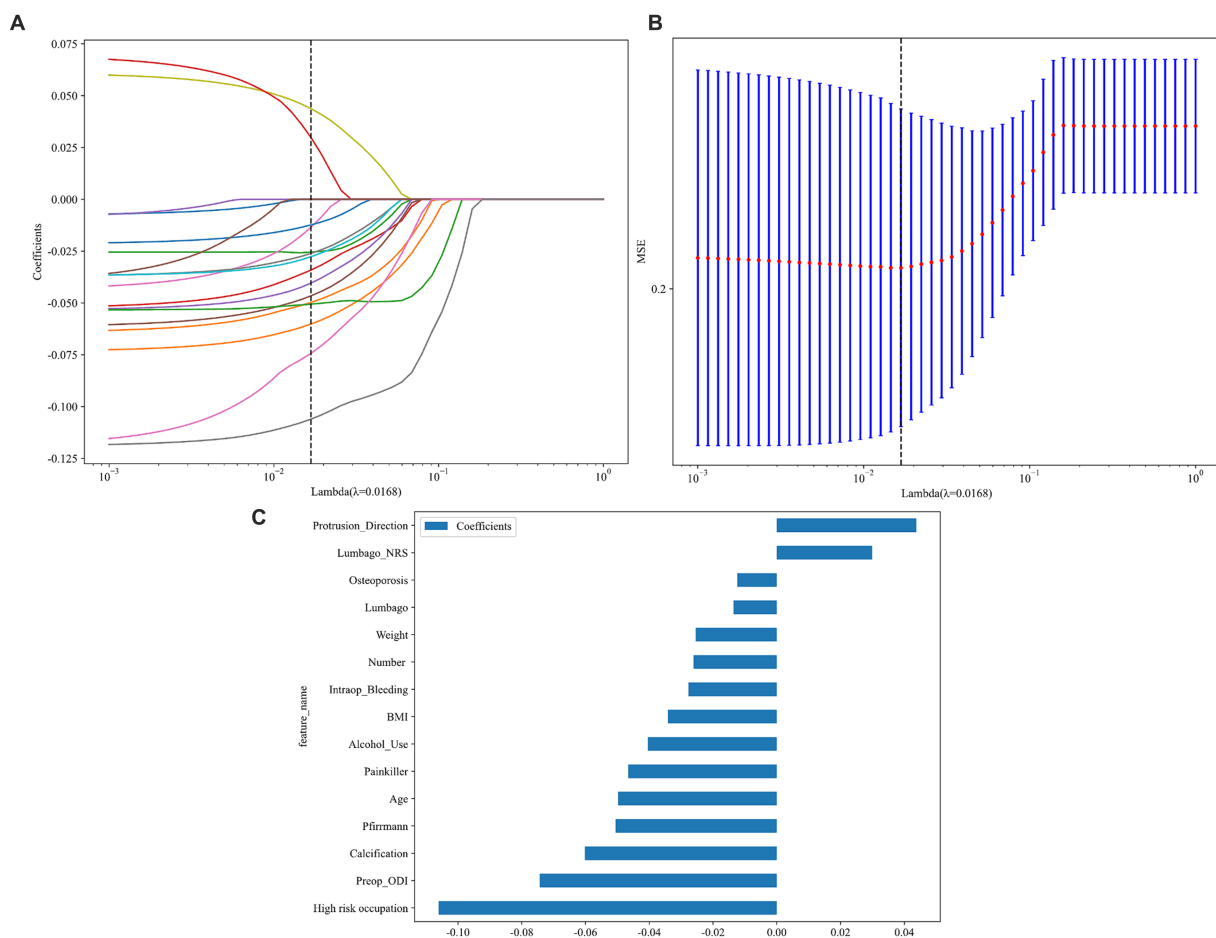


FIGURE 2

The LASSO and MSE in feature engineering and the 15 variables used to input into eight algorithms. (A) The least absolute shrinkage and selection operator (LASSO); (B) A 10-fold-validated mean squared error (MSE); (C) feature weights: variables-score histogram derived from LASSO-selected features.

0.8380, Sensitivity of 0.8040, and Specificity of 0.8600 in test cohort (Figures 3A,B). Additionally, Figure 3C illustrates the superior clinical decision-making capability of MLP (represented by the blue curve) at thresholds greater than 40% (DCA), where it demonstrates a higher net benefit compared to other machine learning algorithms. The Probability Calibration Curve also supports our decision-making process (Figure 3D). Performance comparisons of each model are detailed in Table 2.

Discussion

In the field of surgical treatment for disk herniation, there have been numerous studies investigating the efficacy of different surgical approaches. Specifically, research has focused on the differences in treatment outcomes between TMD and other approaches, such as open microdiscectomy (OMD). Studies have demonstrated that TMD and OMD yield comparable treatment outcomes, but TMD has a significant advantage in reducing intraoperative bleeding (24). Additionally, research has shown that TMD and conventional microdiscectomy (CMD) produce similar outcomes 1 year after

surgery, with TMD not having any advantage in preventing reoperation or dural tears (25). However, limited discussion has been dedicated to patient recovery 1 year after TMD. This study provides a novel approach to addressing the lack of research in this area by implementing machine learning and deep learning techniques to develop predictive models for patient recovery 1 year after TMD.

A limited amount of central data can also be used for deep learning predictive analysis and may be useful for clinical decision making (26). Its comparison of logistic regression models with deep learning models shows the superiority of deep learning performance. Our prediction results demonstrate the advantages of MLP models, especially in terms of AUC values. Of course, close results were obtained for LR, RF, etc., which may be related to the small amount of data, coming from a single clinical study center.

Logistic regression without regularization may be criticized for underfitting, but L2-regularized logistic regression effectively mitigates the risk of overfitting by incorporating a regularization factor or penalty factor, denoted as λ , which multiplies the sum of the squares of all parameters. This reduces the impact of insignificant parameters on the predictive outcome.

TABLE 2 The performance of each model evaluated by accuracy, AUC, sensitivity, specificity, PPV, NPV, Precision, Recall, and F1.

Models	Cohort	Accuracy	AUC	95% CI	Sensitivity	Specificity	PPV	NPV	Precision	Recall	F1
MLP	Train	0.7840	0.8720	0.8347–0.9088	0.7550	0.8050	0.7500	0.8100	0.7500	0.7550	0.7530
RandomForest	Train	0.7620	0.8450	0.8044–0.8854	0.6290	0.8650	0.7830	0.7510	0.7830	0.6290	0.6980
LR	Train	0.7740	0.8350	0.7910–0.8783	0.7550	0.7890	0.7350	0.8070	0.7350	0.7550	0.7450
SVM	Train	0.8690	0.9340	0.9064–0.9615	0.9160	0.8320	0.8090	0.9280	0.8090	0.9160	0.8590
XGBoost	Train	0.8690	0.9380	0.9143–0.9619	0.9580	0.8000	0.7870	0.9610	0.7870	0.9580	0.8640
ExtraTrees	Train	0.7560	0.8350	0.7920–0.8779	0.7970	0.7240	0.6910	0.8220	0.6910	0.7970	0.7400
KNN	Train	0.7530	0.8900	0.8573–0.9223	0.5100	0.9410	0.8690	0.7130	0.8690	0.5100	0.6430
LightGBM	Train	0.7800	0.8820	0.8476–0.9166	0.8740	0.7080	0.6980	0.8790	0.6980	0.8740	0.7760
MLP	Test	0.8380	0.8400	0.7651–0.9143	0.8040	0.8600	0.7890	0.8710	0.7890	0.8040	0.7960
RandomForest	Test	0.7750	0.8310	0.7649–0.8974	0.8040	0.7560	0.6820	0.8550	0.6820	0.8040	0.7380
LR	Test	0.7960	0.8300	0.7550–0.9049	0.7860	0.8020	0.7210	0.8520	0.7210	0.7860	0.7520
SVM	Test	0.7960	0.8160	0.7409–0.8912	0.8210	0.7790	0.7080	0.8700	0.7080	0.8210	0.7600
XGBoost	Test	0.7180	0.8080	0.7381–0.8776	0.8390	0.6400	0.6030	0.8590	0.6030	0.8390	0.7010
ExtraTrees	Test	0.7610	0.8050	0.7294–0.8808	0.8390	0.7090	0.6530	0.8710	0.6530	0.8390	0.7340
KNN	Test	0.7320	0.7990	0.7266–0.8706	0.6610	0.7790	0.6610	0.7790	0.6610	0.6610	0.6610
LightGBM	Test	0.7180	0.7970	0.7257–0.8681	0.6790	0.7440	0.6330	0.7800	0.6330	0.6790	0.6550

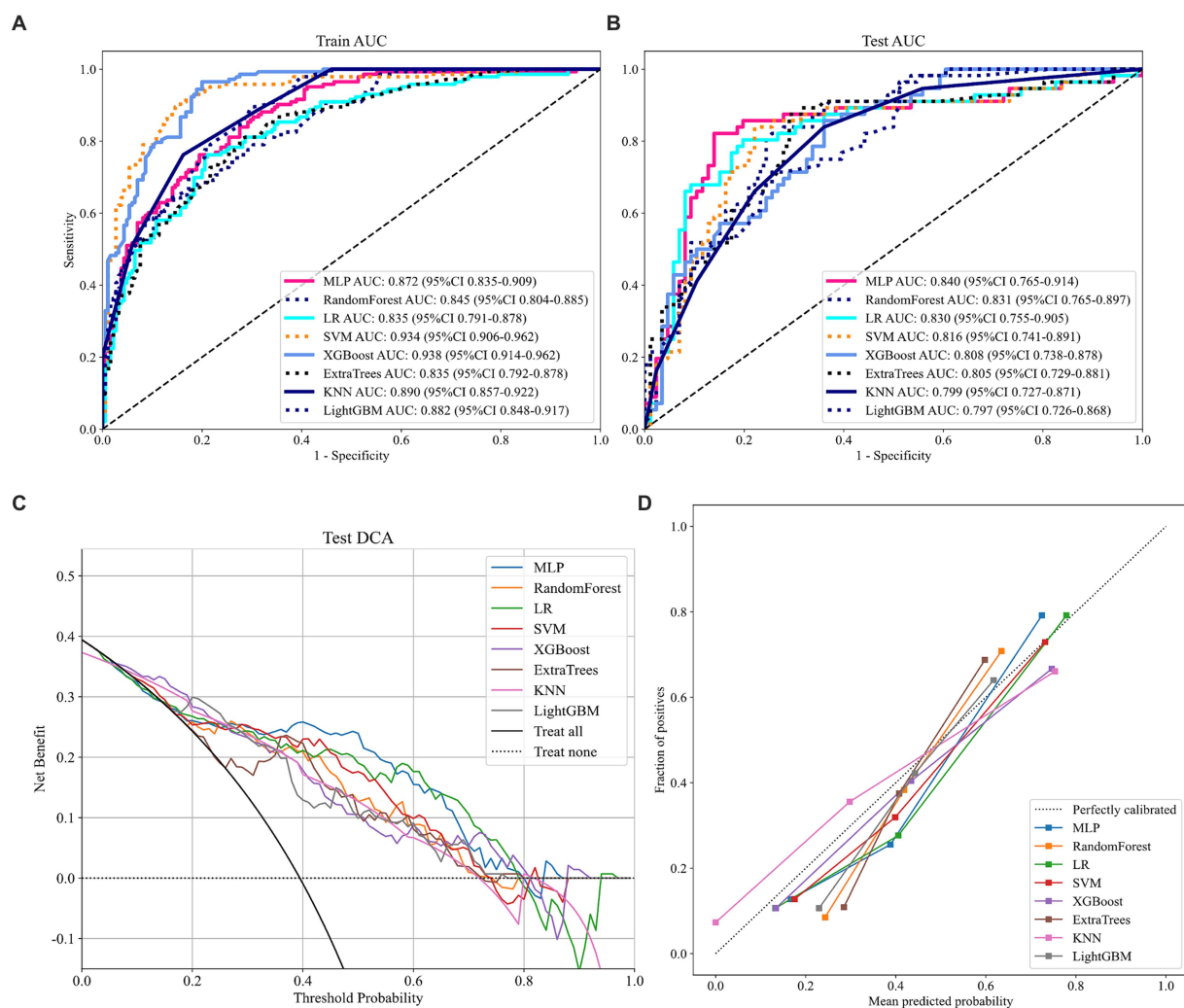


FIGURE 3 Relevant prediction results of the eight models. (A) ROC curve of the train cohort; (B) ROC curve of the test cohort; (C) DCA curve of the test cohort; and (D) Probability calibration curve of the test cohort.

Wang et al. (27) previously utilized a stepwise logistic analysis to filter parameters and select the optimal independent variable based on the minimum Akaike information criterion (AIC) as input for their machine-learning algorithm. Although this study did not utilize this particular machine-learning algorithm, we standardized our data through Z-score normalization. This will reduce the influence of outliers on the model fit. While the correlation matrix heat map is a valuable tool, we acknowledge that the screening process could lead to the exclusion of crucial independent variables. Moreover, the selection of the step probability directly influences the screening outcome. If the step probability is set too low, a substantial number of independent variables may be omitted. On the other hand, increasing the step probability could still result in the loss of important independent variables due to the limited amount of available data, thereby rendering the method meaningless.

Prognostic models offer clinicians an effective means of conveying quantitative risk predictions to patients, thus mitigating information asymmetry to some extent. Accurate determination of surgical indications using such models would enable clinicians to focus their

attention on tasks that cannot be automated. Unfortunately, achieving this goal is currently challenging. The primary obstacle lies in the absence of external model validation, which is necessary to ensure its generalizability to other datasets. The solution may involve conducting multicenter studies to improve the predictive accuracy and generalizability of prognostic models.

In addition to the limitations of data volume, this study has several noteworthy shortcomings. (1) The retrospective nature of the study may have introduced selection bias, undermining the generalizability of the findings. (2) Despite our attempts to collect data on a wide range of variables that may impact the improvement rate of JOA 1 year after surgery, there is a possibility that important variables were overlooked. (3) Due to hardware constraints and the need for machine learning expertise, large-scale generalization of our findings is currently difficult to achieve. (4) The sample size in this study is relatively small, and as a single-center study, additional more data and more centers in the future might enhance our results. Finally, in this study, we used retrospective data for predictive modeling, and in the future, we need to add prospective data for further analysis, which will enhance our clinical evidence.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and was approved by Institutional Review Board (approval no. 2022KY026). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

YC: Methodology, Writing – original draft. FL: Methodology, Writing – original draft. KW: Writing – review & editing. FC: Formal Analysis, Visualization, Writing – review & editing. RuxW: Writing – original draft. ML: Data curation, Writing – original draft. CC: Project administration, Supervision, Writing – review & editing. RuiW: Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2024.1255780/full#supplementary-material>

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Clinical characteristics and predisposing factors of lung metastasis in sacral chordoma: a cross-sectional cohort study of 221 cases

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Introduction: Limited studies are available on the topic of lung metastasis in sacral chordoma. The primary objective of this study was to investigate the prevalence, characteristics, associated factors, and prognosis of lung metastasis in sacral chordoma.

Methods: A total of 221 cases with primary sacral chordoma, all of whom underwent surgical resection at our center, were included in this study. Comprehensive demographic information, imaging findings, and oncological evaluations were collected and thoroughly analyzed. The diagnosis of lung metastasis in the majority of cases was established through radiographic examinations.

Results: The prevalence of lung metastasis in the cohort was 19.5%, with the lung emerging as the predominant site of distant metastasis. Recurrent chordoma cases exhibited a significantly higher lung metastasis rate in comparison to newly diagnosed chordoma cases (33.33% and 12.76%, $p=0.0005$). Patients with lung metastasis had a larger tumor size, a higher proportion of previous sacral chordoma surgeries and a greater likelihood of postoperative recurrence. Associated factors of lung metastasis were tumor size, postoperative recurrence and radiotherapy. Patients with lung metastasis exhibited decreased median overall survival (91 vs. 144 months for those without lung metastasis, $p<0.05$) and recurrence-free survival (27 vs. 68 months, $p<0.001$) times.

Discussion: Lung is the most common site of distant metastasis in sacral chordoma with an incidence rate nearly 20%. Larger tumor size and postoperative recurrence are risk factors for lung metastasis while radiotherapy is a protective factor. Occurrence of lung metastasis in sacral chordoma is a negative prognostic factor.

KEYWORDS

lung metastasis, sacral chordoma, risk factors, survival, recurrence

Introduction

Arising from aberrant notochordal tissue, chordoma constitutes a rare yet locally aggressive neoplasm primarily impacting the axial skeleton, with a predilection for the sacrum, skull base, and mobile spine (1–3). Approximately 30% of chordoma cases manifest in the sacral region (2, 4). Attaining wide resection with a negative surgical margin is deemed imperative for ensuring local control and favorable oncological outcomes in patients with sacral chordoma (5–7). However, the formidable challenges posed by the tumor's substantial volume, its proximity to critical vessels and vital organs, and the intricate anatomy of the pelvic ring render the achievement of wide resection in sacral chordoma cases a formidable undertaking. The incidence of wide resection in patients with sacral chordoma remains constrained, ranging from 25% to 65% (8, 9), thereby predisposing individuals to heightened risks of recurrence and metastasis. Resection of sacral chordoma were subject to postoperative complications. Common postoperative comorbidities of sacral chordoma surgery included infection (wound infection, soft tissue infection, tumor endoprosthesis infection and etc.), wound healing problem, postoperative cerebrospinal fluid leaks, loosening/fracture/displacement of the prosthesis, and postoperative rectal fistula (9).

Research on lung metastasis in chordoma is limited due to its predominantly localized presentation with a low metastatic incidence (2). Moreover, it is crucial to note the variability in reported lung metastatic rates across different studies, with many characterized by small sample sizes (3, 10–12). Chambers et al. reported a 3.7% lung metastasis rate (1 in 27 cases) in chordoma, with primary sites including sacral (62%), vertebral (25%), and cranial (12%) (10). Young et al. demonstrated a 9.6% lung metastasis rate (21 in 219 cases), with primary sites being sacral (61%), vertebral (35%), and cranial (2%) (13). Conversely, Ruggieri et al. reported a 30% lung metastasis rate (16 in 56 cases) specifically in sacral chordomas (14). The variation in proportions of newly diagnosed and recurrent patients among studies contributes to heterogeneity, given the higher malignancy often associated with recurrent chordomas (15). Furthermore, the current literature lacks consensus on whether the lung is the predominant site of distant metastasis in chordoma. While most studies suggest the lung as the primary site (2, 13, 16), a study involving 27 chordoma cases reported bone (38%) and skin (38%) as the most common metastatic sites, with a mere 3.7% lung metastasis rate (10). In this retrospective study of 221 sacral chordoma patients undergoing surgical resection at our center, we aim to address the following questions: (1) What is the lung metastatic rate in sacral chordoma, and is the lung the predominant site of distal metastasis? (2) Does lung metastasis affect the prognosis of sacral chordoma patients? (3) What are the lung metastatic rates for newly diagnosed versus recurrent sacral chordoma, and what distinctions exist? (4) What factors contribute to lung metastasis in sacral chordoma?

Materials and methods

Patients

Between April 2008 and December 2022, 221 primary sacral chordoma patients (149 male and 72 female) underwent surgical resection in our center were enrolled in this study. Institutional review board approval and patient consent were both obtained prior to the initiation of the study. There were 72 (32.6%) patients had recurrent sacral chordoma. 64 (88.9%) patients of them received previous sacrectomy elsewhere prior to the study, and the left 8 (11.1%) patients received surgery at our center prior to the study. Primary surgical resection was performed on the remaining 149 patients at our center following diagnosis. Imaging of the pelvis was performed using enhanced computed tomography (CT) and magnetic resonance imaging (MRI), while the lung was examined using CT. The definite diagnosis was determined based on the needle biopsy results in newly diagnosed patients. Radiotherapy, targeted therapy and chemotherapy were performed in 47, 20 and 1 patients, respectively. The indications for systemic therapy were as follows: (1) metastatic chordoma; (2) dedifferentiated chordoma; (3) positive expression of targeted therapy loci. Patients with multiple metastases could receive chemotherapy. The indications for radiotherapy were as follows: (1) Positive surgical margins of the most recent surgery; (2) Inoperable sacral chordoma after local recurrence;

Surgical procedures

Surgical procedures of sacrectomy at our center have been previously reported (17, 18). The surgical approach used was determined by the size and location of the tumor, with either a combined anterior and posterior approach or a posterior approach alone being employed. Intraoperative hemorrhage control was performed as described previously (19, 20). In the majority of cases (78.3%), a sufficient surgical margin was obtained, as determined by the pathology report.

Follow-up

Follow-up evaluations were conducted at three-month intervals during the first two years, followed by six-month intervals for the subsequent three years, and then annually. The evaluation of each follow-up included X-ray imaging, CT scan or MRI for surveillance of tumor recurrence. Chest CT, bone scan, or PET-CT were performed to detect distal metastasis.

Statistical analysis

Student's *t* test was utilized for normally distributed continuous data, and Mann–Whitney test was utilized for non-normally

distributed continuous data. Categorical variables were assessed using X^2 or Fisher's exact tests. Receiver operating characteristic (ROC) curve analysis was employed to determine the cutoff value for continuous variables. Variables with a p value of <0.1 in the bivariate analysis were entered into a binary logistic regression model for multivariate analysis. Survival analysis was performed using Kaplan-Meier curves and the log-rank test. A p -value <0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism 9.

Results

Baseline data

This study encompassed a cohort of 221 individuals diagnosed with primary sacral chordoma, with a male predominance of 67.4% ($n=149$) and a female representation of 32.6% ($n=72$) (Table 1). The mean follow-up time of the cohort was 52.6 ± 48.8 months (12 to 252 months). The mean age (and standard deviation [SD]) of the cohort was 57.4 ± 12.0 years, and the average duration from symptom onset to presentation was 15.7 ± 19.1 months. Postoperative radiotherapy was administered to 21.3% of patients ($n=47$), while preoperative radiotherapy was not routinely performed in our center. Targeted therapy, specifically imatinib for cases positive for PDGFR-beta on immunohistochemistry, was undertaken by 20 patients. One patient with metastatic dedifferentiated chordoma received chemotherapy. 83.7% of patients underwent *en bloc* resection with the other received fragmented resection. There were eleven cases of breaking tumoral capsule during operation. An adequate surgical margin was accomplished in 78.3% of cases ($n=173$), with an intralesional margin achieved in 21.7% ($n=48$) of cases. Notably, 67.4% of patients were newly diagnosed, whereas the remaining 32.6% had undergone prior surgical interventions and had a history of recurrence.

Prevalence of lung metastasis

Within the cohort, 43 cases (19.5%) exhibited lung metastasis, as illustrated in Figure 1. Notably, 39 of these cases developed lung metastasis postoperatively, constituting 90.7% of lung metastasis occurrences. Diagnosis of lung metastasis was primarily established through chest CT scans, with one patient undergoing surgical excision for pathological confirmation. The mean duration between surgery and postoperative lung metastasis was 30.0 ± 37.8 months. Patients with lung metastasis demonstrated a larger tumor size (93.6 ± 39.2 vs. 79.3 ± 36.8 , $p=0.033$), a higher incidence of prior sacral chordoma surgeries (55.8% vs. 27.0%, $p<0.001$), and a greater likelihood of postoperative recurrence (86.0% vs. 45.6%, $p<0.001$) (Table 2). Notably, patients with lung metastasis also had higher proportion of receiving radiotherapy (39.5% vs. 16.6%, $p=0.003$) as

TABLE 1 Demographic and clinical characteristics of 221 cases of sacral chordoma.

Variables	Value
Sex (no. [%])	
Male	149 (67.4)
Female	72 (32.6)
Age* (yr)	57.4 ± 12.0
Height* (cm)	166.7 ± 10.2
Weight* (kg)	68.3 ± 11.1
Body mass index* (kg/m^2)	24.4 ± 3.1
Time from symptom onset to presentation* (month)	15.7 ± 19.1
Tumor size* (mm)	82.4 ± 37.6
Involved spinal column levels	
Sacrum + Lumbar	12 (5.4)
Sacrum alone	74 (33.5)
Sacrum + Coccyx	130 (58.8)
Coccyx alone	5 (2.3)
Histology (no. [%])	
Typical	214 (96.8)
Chondroid	3 (1.4)
Dedifferentiated	4 (1.8)
Ki-67* (%)	9.2 ± 6.9
Radiotherapy (no. [%])	47 (21.3)
Previous surgery [#] (no. [%])	
No/Newly diagnosed	149 (67.4)
Yes/Recurrent	72 (32.6)
Postoperative recurrence [§] (no. [%])	
No	98 (44.3)
Yes	123 (55.7)
En-bloc resection (no. [%])	
No	36 (16.3%)
Yes	185 (83.7%)
Surgical approach (no. [%])	
Combined anterior and posterior approach	21 (9.5%)
Posterior approach	200 (90.5%)
Surgical margin (no. [%])	
Inadequate	48 (21.7)
Adequate	173 (78.3)
Brachyury expression (no. [%])	
Negative	0 (0)
Positive	221 (100)
Lung metastasis (no. [%])	
No	178 (80.5)
Yes	43 (19.5)

(Continued)

TABLE 1 Continued

Variables	Value
Primary/Secondary lung metastasis (no. [%])	
Primary	4 (9.3)
Secondary	39 (90.7)
Time to development of lung metastasis* (month)	30.0 ± 37.8

*The values are given as the mean and standard deviation. [#]Patients who had previous surgery of sacral chordoma and were presented due to local recurrence. [§]Patients who underwent surgical resection of sacral chordoma at our center during the study period and had local recurrence, no matter whether they had previous surgery of sacral chordoma or not.

shown in Table 2. In the 47 patients who received radiotherapy, the resection statuses were 16 inadequate margins and 31 adequate margins. 22 patients had previous surgery of sacral chordoma and were presented due to local recurrence. After surgical treatment at our center, 40 patients experienced postoperative local recurrence.

Significant disparities in the prevalence of lung metastasis were observed between newly diagnosed and recurrent chordoma patients, with the latter group exhibiting a substantially higher rate (33.33% vs. 12.76%, $p=0.0005$) (Table 3; Figure 2). An analysis of the impact of postoperative time on lung metastasis revealed a similarity in prevalence between 1-2 years and 3-4 years postoperatively, with an increase noted in cases beyond 5 years (Odds ratio (OR) 2.109, 95% CI [1.058, 4.182], $p=0.0414$) (Figure 3).

Further investigation into the influences of local recurrence and postoperative time on the prevalence of lung metastasis indicated that local recurrent sacral chordoma patients consistently displayed a significantly higher prevalence of lung metastasis, both within 5 years and beyond 5 years postoperatively (Figure 4). For patients with newly diagnosed sacral chordoma, the follow-up period was the time interval after surgical resection at our center. For patients with local recurrent sacral chordoma, the follow-up period only considered the time interval after resection of the local recurrence. Interestingly, the prevalence of lung metastasis over 5 years postoperatively was statistically comparable to that within 5 years in both newly diagnosed and local recurrent patients, suggesting that

postoperative time did not directly impact lung metastasis in sacral chordoma patients. Subsequently, our proposition posits that the observed effect of postoperative time on the prevalence of lung metastasis may stem from variations in the local recurrence rate across different time periods, as local recurrence rates were notably higher beyond 5 years postoperatively compared to within 5 years (OR 1.940, 95% CI [1.091, 3.569], $p=0.0382$, Figure 5). In summary, our comprehensive analysis highlights that local recurrence significantly influences the prevalence of lung metastasis, while postoperative time does not exert a direct impact on lung metastasis in both newly diagnosed and local recurrent sacral chordoma patients.

Factors associated with lung metastasis

A bivariate analysis was conducted to explore potential factors associated with lung metastasis in the cohort, revealing significant associations with tumor size ≥ 93 mm (OR=2.48, 95% confidence interval [CI] [1.20, 5.13], $p=0.014$), radiotherapy (OR=0.25, 95%CI [0.12, 0.54], $p<0.001$), previous surgery (OR=2.37, 95%CI [1.14, 4.91], $p=0.019$), and postoperative recurrence (OR=6.36, 95%CI [2.68, 17.62], $p<0.001$) (Table 4). Patients with local recurrence had a higher proportion of positive resection margins (31.7% vs. 11.2%, $p=0.0003$). Subsequent multivariate analysis affirmed tumor size ≥ 93 mm ($p=0.015$) and postoperative recurrence ($p=0.003$) as risk factors linked to lung metastasis, while radiotherapy emerged as a protective factor ($p=0.016$).

Prognosis of sacral chordoma with lung metastasis

In our cohort, 31 patients (14%) experienced mortality, while 190 patients (86%) survived. The average survival time was 93.3 ± 52.2 months for the 31 patients who experienced mortality. Within the deceased group, 13 cases (42%) succumbed to lung metastasis,

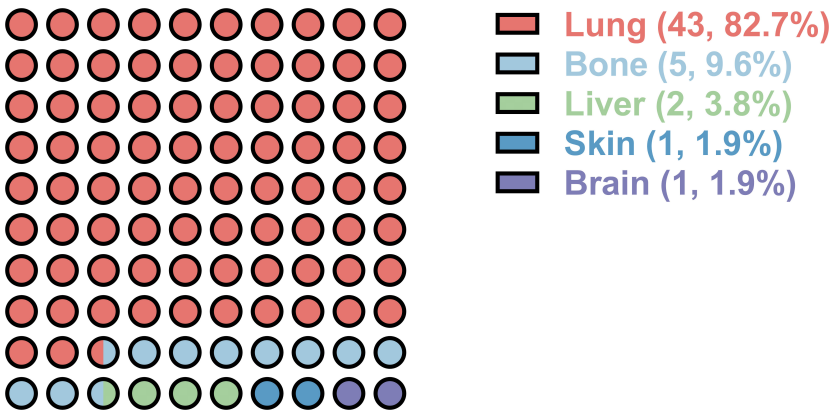


FIGURE 1
Distant metastatic organ distribution of postoperative sacral chordoma. Numbers in the bracket represent the number and percentage of the metastatic organ, respectively.

TABLE 2 Comparison of demographic and clinical characteristics between patients with and without lung metastasis.

Variables	With lung metastasis (n=43)	Without lung metastasis (n=178)	p-value
Sex (no. [%])			
Male	29 (67.4)	119 (66.9)	>0.999
Female	14 (32.6)	59 (33.1)	
Age* (yr)	56.7 ± 12.8	57.6 ± 11.9	0.586
Height* (cm)	167.8 ± 8.4	166.8 ± 7.7	0.685
Weight* (kg)	66.9 ± 11.2	68.5 ± 11.1	0.213
Body mass index (kg/m2) *	23.7 ± 3.0	24.6 ± 3.1	0.352
Time from symptom onset to presentation* (month)	14.1 ± 12.5	16.1 ± 20.2	0.124
Tumor size* (mm)	93.6 ± 39.2	79.3 ± 36.8	0.033*
Involved spinal column levels			0.574
Sacrum + Lumbar 12	2 (4.7%)	10 (5.6%)	
Sacrum alone 74	16 (37.2%)	58 (32.6%)	
Sacrum + Coccyx 130	23 (53.5%)	107 (60.1%)	
Coccyx alone 5	2 (4.7%)	3 (1.7%)	
Histology (no. [%])			0.410
Typical	41 (95.3%)	173 (97.2%)	
Chondroid	1 (2.3%)	2 (1.1%)	
Dedifferentiated	1 (2.3%)	3 (1.7%)	
Radiotherapy (no. [%])	17 (39.5)	30 (16.6)	0.003*
Previous surgery [#] (no. [%])			<0.001*
No/Newly diagnosed	19 (44.2)	130 (73.0)	
Yes/Recurrent	24 (55.8)	48 (27.0)	
Surgical approach (no. [%])			0.257
Combined anterior and posterior approach	6 (14.0%)	15 (8.4%)	
Posterior approach	37 (86.0%)	163 (91.6%)	
Postoperative recurrence ^{&} (no. [%])			<0.001*
No	6 (14.0)	97 (54.4)	
Yes	37 (86.0)	81 (45.6)	
Surgical margin (no. [%])			0.145
Inadequate	13 (30.2)	34 (19.5)	
Adequate	30 (69.8)	143 (80.5)	

*The values are given as the mean and standard deviation. [#]Patients who had previous surgery of sacral chordoma and were presented due to local recurrence. [&]Patients who underwent surgical resection of sacral chordoma at our center during the study period and had local recurrence, no matter whether they had previous surgery of sacral chordoma or not.

TABLE 3 Differential lung metastasis rates in newly diagnosed and recurrent sacral chordoma.

Lung metastasis	Newly diagnosed (n=149)	Recurrent (n=72)	p-value
No	130 (87.24)	48 (66.67)	0.0005
Yes	19 (12.76)	24 (33.33)	

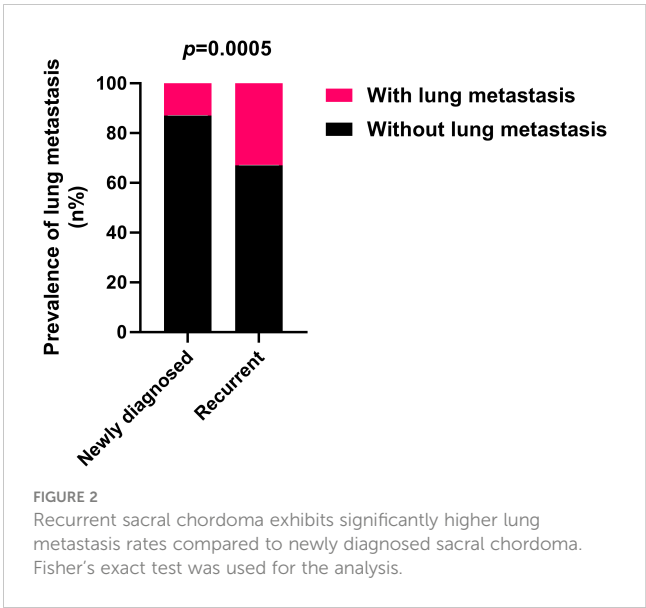


FIGURE 2 Recurrent sacral chordoma exhibits significantly higher lung metastasis rates compared to newly diagnosed sacral chordoma. Fisher's exact test was used for the analysis.

all of whom had undergone postoperative recurrence, with recurrence instances reaching up to 5 times. The median overall survival (OS) and recurrence-free survival (RFS) times were 132 and 48 months, respectively. The 5-year OS rate in the overall cohort was 78.4%. Notably, sacral chordoma patients with lung metastasis exhibited significantly shorter OS (91 months vs. 144 months, hazard ratio 3.464, 95% CI [1.329, 9.028], $p<0.05$) and RFS (27 months vs. 68 months, hazard ratio 3.881, 95% CI [2.305, 6.532], $p<0.001$) times compared to those without lung metastasis (Figure 6). It was observed that strategies incorporating additional target therapy, radiotherapy, or a combination of target therapy with radiotherapy did not yield improvements in overall prognosis for patients in the cohort, irrespective of the presence or absence of lung metastases ($p>0.05$, Supplementary Table 1).

Discussion

Limited studies have delved into the patterns of lung metastasis in sacral chordoma, primarily owing to the tumor's characteristic slow growth and local aggressiveness. The metastatic patterns of chordoma in previous clinical series have exhibited variability across different studies. While the majority of research has asserted the lung as the most common metastatic site of chordoma (2, 13, 16), a dissenting viewpoint emerged in one study suggesting the skin as the predominant metastatic site (10). In alignment with the prevailing consensus in most previous investigations, our current study affirms that the lung constitutes the most frequent metastatic site in sacral chordoma, encompassing 82.7% of distal metastasis occurrences within the cohort. To our knowledge, this study represents the largest examination of lung metastasis in primary, postoperative sacral chordoma within the existing literature.

In contrast to osteosarcoma and Ewing's sarcoma, the consideration of lung metastasis in chordoma has historically

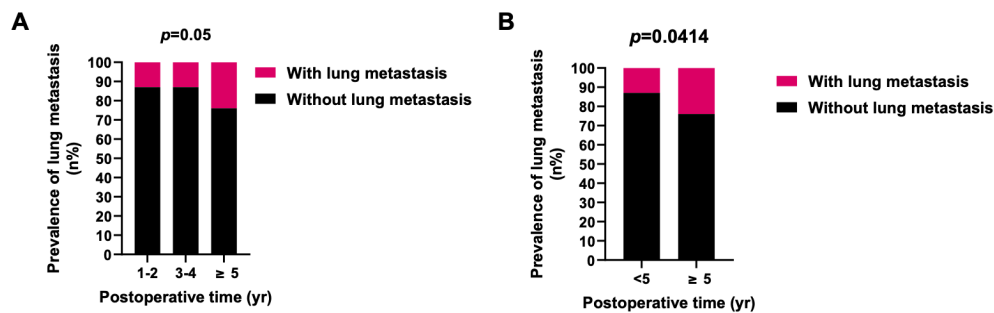


FIGURE 3

Prevalence of lung metastasis in different periods after surgery. (A) The prevalence of lung metastasis in 1-2 and 3-4 years postoperatively was similar, and the prevalence of lung metastasis in ≥ 5 years was higher. (B) The prevalence of lung metastasis in ≥ 5 years after surgery was significantly higher than <5 years. χ^2 test was used for the analysis.

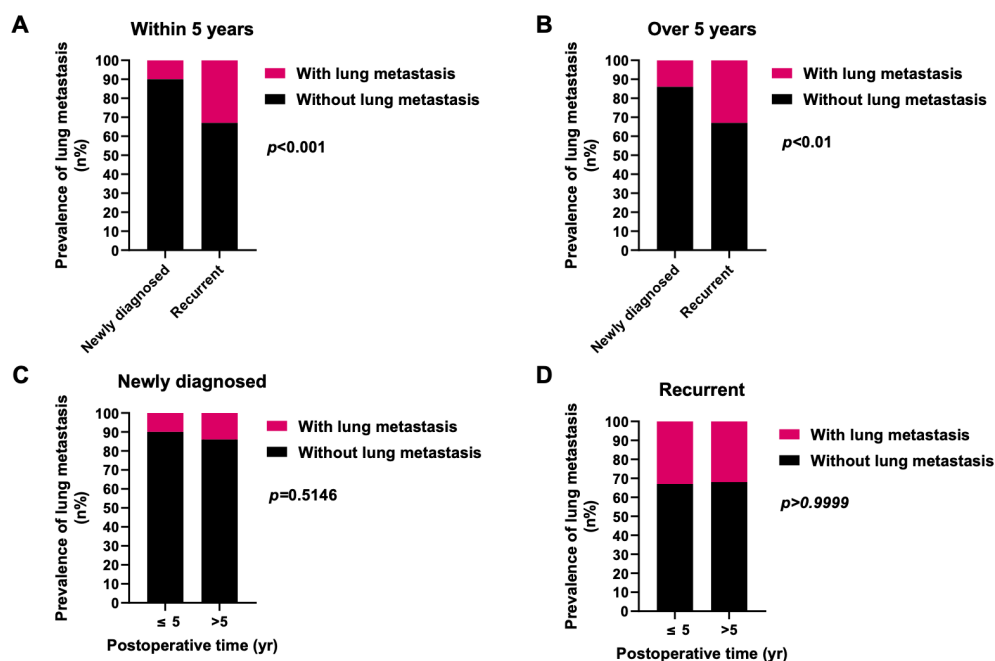


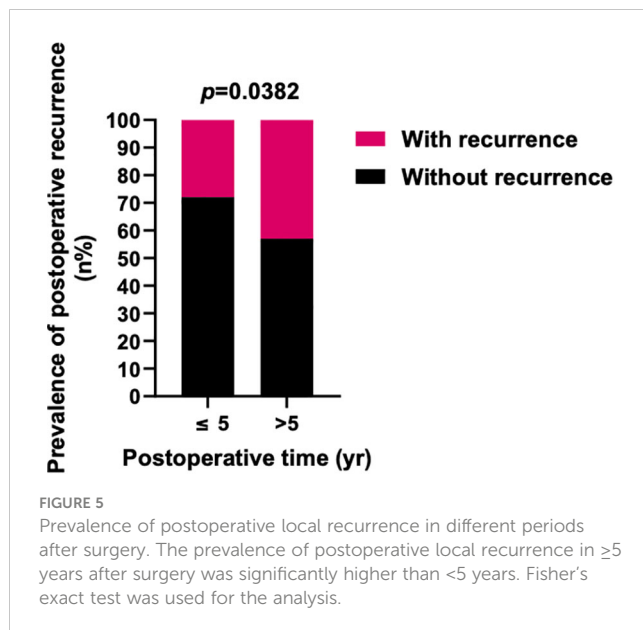
FIGURE 4

Effects of local recurrence and postoperative time on the prevalence of lung metastasis. (A, B) The prevalence of lung metastasis in local recurrent patients was significantly higher than newly diagnosed patients within 5 years (A) as well as over 5 years (B) postoperatively. (C, D) In both newly diagnosed (C) and local recurrent (D) patients, the prevalence of lung metastasis over 5 years postoperatively was statistically similar to those within 5 years. Fisher's exact test was used for the analysis.

been overlooked due to its predominantly localized aggressiveness. Additionally, the limited morbidity of sacral chordoma has resulted in a scarcity of cases in most previous studies. The reported lung metastasis rates in the literature have ranged widely from 3.7% to 40% (2, 3, 9, 10, 13, 16, 21), with these data being confounded by small sample sizes. In our study, encompassing 221 sacral chordoma patients, the prevalence of lung metastasis was determined to be 19.5%, with distinct rates observed for newly diagnosed (12.76%) and recurrent patients (33.33%). Our prior research revealed that the third and fourth years post-surgery were the most susceptible periods for tumor recurrence, with conditional survival gradually decreasing in the initial four years and subsequently increasing after the fifth year (9). Consequently, our investigation into the prevalence of lung metastasis spanned an

extended timeframe, analyzing the postoperative lung metastasis rate over time. The results disclosed a significant increase in the prevalence of lung metastasis beyond 5 years postoperatively. Importantly, we established that postoperative time did not exert a direct influence on lung metastasis, but rather, its impact was likely mediated through the occurrence of postoperative recurrence. However, it is imperative to validate this hypothesis in other cohorts of sacral chordoma patients for robust confirmation.

Recurrence emerges as a pivotal factor influencing the prevalence of lung metastasis in sacral chordoma. The study by Young et al. revealed that metastatic disease occurred 2.5 times more frequently in recurrent chordoma patients compared to those without recurrence (13). A systematic review, encompassing nine surgical and seven radiotherapy articles, further affirmed that



recurrent chordoma correlated with a predominantly poor outcome, irrespective of the chosen treatment strategy (15). In 2017, the global chordoma patient advocacy group published a consensus outlining the optimal approach to recurrent chordoma, highlighting the worsening clinical outcomes associated with recurrent occurrences (22, 23). Consistent with these previous findings, our study demonstrated a significantly higher lung metastasis rate among local recurrent patients. Importantly, this trend persisted even when the postoperative time was held constant between newly diagnosed and local recurrent patients. Therefore, the influence of local recurrence on the prevalence of lung metastasis in sacral chordoma appears to be independent of postoperative time. The observed variations in the prevalence of lung metastasis between newly diagnosed and local recurrent

patients may stem from the increased malignancy typically associated with local recurrent chordoma cases.

The identification of risk factors for lung metastasis is essential for guiding the follow-up care of high-risk patients. However, the literature on risk factors for lung metastasis in sacral chordoma is limited due to the scarcity of previous studies on this topic. Bergh et al. demonstrated that recurrence increased the risk for metastasis by 23-fold, while inadequate surgical margin did not exert an influence on metastasis (24). Yang et al. reported that local recurrence was the sole risk factor for metastasis ($p=0.016$) (25). Consistent with these prior findings, our study identified postoperative recurrence as a significant risk factor for lung metastasis in our cohort ($p=0.003$). Another identified risk factor was tumor size ≥ 93 mm ($p=0.015$), which was not previously recognized as a risk factor for lung metastasis. Additionally, radiotherapy ($p=0.016$) emerged as a protective factor against lung metastasis in our study. However, patients with lung metastasis also had higher proportion of receiving radiotherapy. The higher proportion of radiotherapy in patients with lung metastasis was due to the higher proportion of local recurrence and positive surgical margin, which were both indication for radiotherapy. It is noteworthy that the differences in identified risk factors between the current study and previous studies may be attributed to variations in sample sizes. Previous studies typically included a maximum of 17 cases of sacral chordoma patients with lung metastasis, whereas our study encompassed a larger cohort of 43 cases with lung metastasis. This disparity in sample sizes could contribute to the nuanced understanding of risk factors in the current study.

The occurrence of lung metastasis in sacral chordoma patients signifies disease progression and has a detrimental impact on the patient's prognosis (24, 25). Consistent with findings from prior studies, our study revealed that patients with lung metastasis experienced significantly worse OS and RFS times compared to those without metastasis. It is noteworthy that in some cases, the

TABLE 4 Risk factors for lung metastasis in the cohort.

Variables	Bivariate analysis			Multivariate analysis	
	OR	95% CI	p-value	OR (95% CI)	p-value
Sex	1.10	0.53, 2.42	0.799		
Age	1.00	0.97, 1.03	0.862		
Time from symptom onset to presentation* (month)	1.00	0.99, 1.03	0.659		
Tumor size (mm)	0.99	0.98, 1.00	0.048*		
Tumor size ≥ 93 mm†	2.48	1.20, 5.13	0.014*	2.67 (1.22, 5.95)	0.015*
Chemotherapy	0.43	0.16, 1.32	0.118		
Radiotherapy	0.25	0.12, 0.54	$<0.001^*$	0.36 (0.16, 0.82)	0.016*
Previous surgery	2.37	1.14, 4.91	0.019*	0.87 (0.36, 2.12)	0.763
Postoperative recurrence	6.36	2.68, 17.62	$<0.001^*$	5.17 (1.78, 16.47)	0.003*
Surgical margin	1.29	0.53, 2.92	0.552		

* $p<0.05$. †ROC curve analysis resulted in a tumor size of 93 mm as the cutoff value.

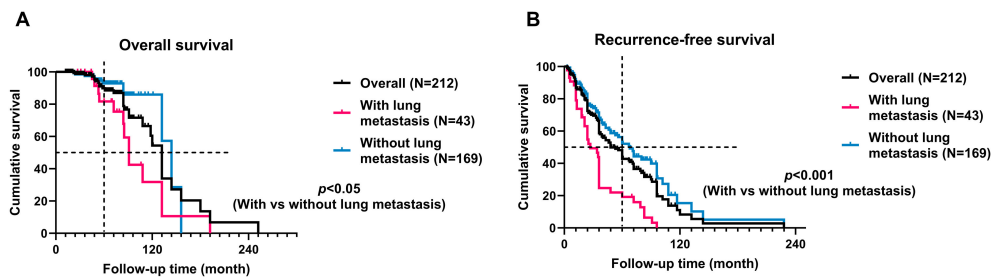


FIGURE 6

Kaplan-Meier curves with the log-rank test of the overall (A) and recurrence-free (B) survival of patients with lung metastasis compared to patients without lung metastasis. Patients with lung metastasis had significantly worse oncological outcomes.

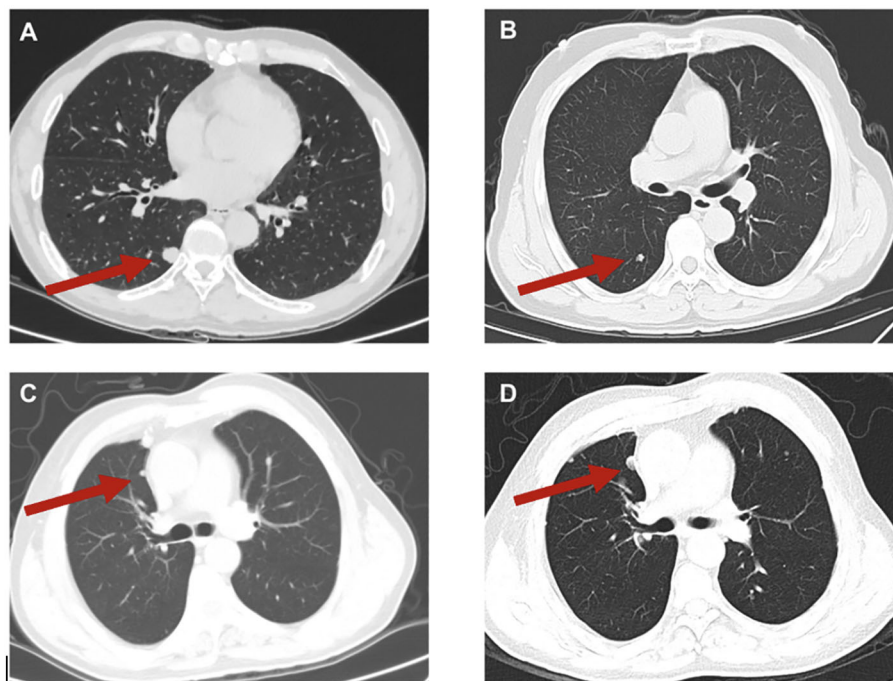


FIGURE 7

Typical images of lung metastases (A, B) and of progression of lung metastases (C, D) in sacral chordoma patients. The red arrow indicated the lung metastases. (D) represented the progression of lung metastasis compared to (C) in an 8-month interval.

lung metastases of sacral chordoma may exhibit rapid progression (Figure 7), and surgical intervention for resectable lesions remains a viable treatment option. Despite chordoma being characterized as a slow-growing tumor, our study underscores the importance of regular and long-term postoperative follow-ups. Lung metastasis can manifest even after an extended period postoperatively, posing a continuous threat to clinical prognosis. Hence, maintaining vigilance through regular postoperative follow-up is crucial for timely identification and management of lung metastasis in sacral chordoma patients.

The present study is subject to several limitations that warrant consideration. Firstly, the retrospective nature of the study makes it susceptible to selection and recall bias, potentially impacting the generalizability of the conclusions. The findings from this study

may not be entirely consistent with those from other clinical series due to inherent biases associated with retrospective analyses. Secondly, the inclusion of cases from a single institute introduces the possibility of referral bias, limiting the external validity of the results. The patient population from a single institution may not be entirely representative of the broader demographic and clinical spectrum. Thirdly, the cohort includes patients who underwent surgery elsewhere and were subsequently admitted to our institute due to local recurrence. Consequently, the clinical data for these patients may be incomplete, introducing a potential source of bias and limiting the comprehensiveness of the study findings.

In conclusion, the prevalence of lung metastasis of sacral chordoma in this cohort was 19.5%. Recurrent chordoma had a significantly higher lung metastasis rate than newly diagnosed

chordoma (33.33% and 12.76%, respectively). Postoperative time did not influence lung metastasis directly. The risk factors for lung metastasis in sacral chordoma were tumor size and postoperative recurrence, and the protective factor was radiotherapy. Patients with lung metastasis had significantly worse oncological outcomes than those without.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The Ethics Committee of Peking University People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

QS: Investigation, Writing – original draft. WG: Conceptualization, Resources, Writing – review & editing. SY: Data curation, Writing – original draft, Formal analysis. JX: Formal analysis, Writing – review & editing. TJ: Methodology, Supervision, Writing – review & editing. XT: Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2024.1416331/full#supplementary-material>

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Effects of suspension exercise training in the treatment of lumbar disk herniation: a systematic review and meta-analysis

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Objective: The study aimed to systematically evaluate the efficacy of suspension exercise training (SET) in the treatment of lumbar intervertebral disk herniation and provide a scientific basis for clinical treatment.

Methods: Databases such as CNKI, Chinese Wanfang, PubMed, Cochrane, the Web of Science, and Embase were searched up to June 2024. A quality assessment was performed using the Cochrane Collaboration's risk-of-bias guidelines, and a meta-analysis was conducted using RevMan 5.4 and Stata 17.0.

Results: A total of 11 studies involving 943 patients were included. Suspension exercise training significantly improved the lumbar disk herniation (LDH) visual analog scale (VAS) score (mean difference (MD) = -0.96; 95% confidence interval (CI), -1.10 to -0.82; $p < 0.00001$, $I^2 = 23\%$), the Japanese Orthopedic Association (JOA) score (MD = 3.29, 95% CI, 1.67 to 4.90; $p < 0.0001$, $I^2 = 92\%$), and the Oswestry Disability Index (ODI) score (MD = -5.41, 95% CI, -7.41 to -3.40; $p < 0.00001$, $I^2 = 86\%$). Subgroup analysis of the JOA score showed better efficacy with suspension exercise training combined with traditional Chinese medicine (TCM) (MD = 4.29, 95% CI, 2.73 to 5.86; $p < 0.00001$, $I^2 = 80\%$) compared to suspension exercise training combined with non-TCM (MD = 0.96, 95% CI, 0.49 to 1.43; $p < 0.0001$, $I^2 = 0\%$).

Conclusion: Suspension exercise training significantly improved the VAS score, JOA score, and ODI score of the patients with lumbar disk herniation; however, there was a high degree of heterogeneity in the JOA score and ODI score. Further validation is needed in the future for different populations with lumbar disk herniation, the specific locations of its occurrence, and the combined modality of suspension exercise training.

Systematic review registration: <https://www.crd.york.ac.uk/prospero/>, identifier CRD42024554074.

KEYWORDS

suspension exercise training, lumbar disc herniation, pain, Meta-analysis, review

1 Introduction

Lumbar disk herniation (LDH) is a common clinical spinal disorder in which the fibrous annulus of the lumbar disk partially or completely ruptures due to various causes. This rupture causes the nucleus pulposus tissue to protrude backward, irritating or compressing the nerve roots and cauda equina (1). Low back pain and neurological

dysfunction are the main clinical manifestations (2). In recent years, the incidence of LDH has been increasing annually and shows a trend toward younger age groups (3). It is estimated that approximately 2–3% of the world's population experiences LDH (4), which mainly affects adults between the ages of 20 and 50 years (3). Intensive work, long hours, sedentary behavior, and prolonged standing are considered the main causes of LDH. Difficulties in standing, walking, and performing simple tasks in patients with LDH have significantly impacted global productivity, public health, and the quality of life for those affected (5, 6). The United States spent up to \$4 billion on treating LDH through medication and surgery in 2015 alone (7).

The treatment of LDH can be broadly categorized into surgical and non-surgical approaches. Although surgical treatments can provide rapid pain relief, they are associated with significant drawbacks, such as postoperative complications, technical challenges, a high risk of reoperation, and substantial costs (8–10). Consequently, 80–85% of patients opt for non-surgical treatments (11).

Non-surgical treatment options for LDH include a variety of therapeutic approaches aimed at alleviating symptoms and improving function without the need for invasive procedures. These options include physical therapy, pharmacological treatments, chiropractic care, and acupuncture (12–14). Suspension exercise training (SET) is emerging as a promising non-invasive therapy for treating skeletal and muscular disorders, including LDH. SET is simple, easy to perform, painless, relatively inexpensive, and effective (10). Despite its potential benefits, there has been no comprehensive systematic review or meta-analysis specifically evaluating the efficacy of SET for treating LDH. Our study aimed to provide a new option for the treatment of LDH.

2 Methods

This study was registered in PROSPERO (CRD42024554074) and strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (15).

2.1 Literature search and selection

We searched the CNKI, Chinese Wanfang, PubMed, Cochrane, Web of Science, and Embase databases for Chinese and English literature up to June 2024. The search terms included “sling exercise,” “suspension exercise,” and “LDH.” The inclusion criteria were as follows: (1) treatment involving suspension exercise; (2) patients diagnosed with LDH; (3) study design as a randomized controlled trial or a clinical trial; and (4) the visual analog scale (VAS) score, Japanese Orthopedic Association (JOA) score, and Oswestry Disability Index (ODI) score of suspension exercise for LDH. The exclusion criteria were as follows: (1) no control group in the trial; (2) no data on baseline or endpoint outcomes; (3) patients with psychiatric disorders; and (4) reviews, dissertations, or conference papers.

Duplicates were removed using EndNote X9 software. Two authors (SL and XX) independently read the titles and abstracts of the literature to determine whether the inclusion criteria were met. The studies that initially met the inclusion criteria were read in full to determine final inclusion. For disagreements regarding the studies, a third author (HY) was involved to help determine inclusion through discussion.

2.2 Data extraction and quality assessment

Data extraction from the final included studies was performed independently by two authors (SL and HY), and the extracted information included the first author, year of publication, basic information about the participants, types of interventions, intervention duration, outcome indicators, and follow-up time.

The Cochrane Collaboration's risk-of-bias guidelines (16) were used to evaluate the quality of the included studies. The guidelines included the following: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessments, (5) incomplete outcome data, (6) selective reporting, and (7) other bias. The quality of the studies was evaluated independently by two authors. In case of a disagreement, a third author was involved in discussions until an agreement was reached.

2.3 Types of outcome indicators

The primary outcome indicators included the visual analog scale (VAS) (17), and the secondary outcome indicators included the Japanese Orthopedic Association (JOA) (18) and Oswestry Disability Index (ODI) (19).

2.4 Data synthesis and statistical analysis

All outcome indicators in this study were continuous variables measured on the same rating scale and were analyzed using mean difference (MD) and a 95% confidence interval (CI) as effect sizes. The effect size resulting from the meta-analysis provided a statistically standardized representation of the quantitative results of each study. It was calculated based on the mean pre-post change in the experimental group minus the mean pre-post change in the comparison group and then divided by the pooled pretest standard deviation. The meta-analysis was performed using RevMan 5.4 and Stata 17.0. Heterogeneity was quantified using the I^2 statistic, and a fixed effects model was employed if the difference in the heterogeneity test was not statistically significant ($I^2 < 50\%$; $p > 0.05$). Otherwise, a random effects model was applied. Subgroup and sensitivity analyses were performed to explore the sources of heterogeneity for the outcome indicators. The subgroup analyses were performed according to the type of interventions, while the sensitivity analyses were performed by removing each study item to assess the reliability and consistency of the results. Publication bias was assessed using funnel plots and Egger's asymmetry test for outcome measures with more than 10 included studies. All statistical significance levels were set at $\alpha = 0.05$.

3 Results

3.1 Search results

A total of 287 studies were identified through database searches, and 208 studies remained after removing duplicates using EndNote X9. Two authors reviewed the titles and abstracts of the studies

according to the inclusion and exclusion criteria for preliminary screening. In case of a disagreement between the two authors, a third author was involved in the discussion and decided whether to include a study. A total of 189 irrelevant studies were excluded, leaving 19 articles that were read in full. An additional eight articles that did not meet the inclusion criteria were excluded, resulting in a final total of 11 articles that were included in the meta-analysis. The literature screening process is shown in [Figure 1](#).

3.2 Basic characteristics of the included studies

This meta-analysis included 11 studies (20–30), involving 943 patients—472 in the test group and 471 in the control group. There were 463 male participants and 397 female participants, with two studies not reporting the sex of the participants. The mean age of the patients ranged from 37.2 to 58.6 years, with one study not reporting the mean age. The intervention period ranged from 2 to 8 weeks. The outcome indicators included the VAS, JOA, and ODI scores. Six studies reported follow-up, while five did not (see [Table 1](#)).

3.3 Quality evaluation results

This meta-analysis used the Cochrane Collaboration's risk-of-bias guidelines to assess the quality of the included studies. Regarding random sequence generation, 11 studies were assessed as low risk because they all reported random allocation using the

random number expression method. Regarding allocation concealment, 11 studies reported that the method used for allocation concealment was not clearly stated, and thus they were assessed as uncertain risk. In terms of blinding of participants and personnel, one study that indicated that the intervention was conducted uniformly was assessed as uncertain risk, while 10 studies that did not report implementation blinding were assessed as high risk. Regarding blinding of outcome assessments, two studies that reported that the blinding of outcome assessments was performed by uniform professionals were assessed as uncertain risk, while nine studies that did not report on the blinding of outcome assessment were assessed as high risk. In terms of incomplete outcome data, six studies with complete outcome data were assessed as low risk, while five studies were assessed as uncertain risk for not reporting follow-up. In terms of selective reporting, all 11 studies that reported findings were assessed as low risk. In terms of other biases, all 11 studies were assessed as low risk, with no additional biases identified. The results of the quality assessment are shown in [Figure 2](#).

3.4 Meta-analysis results

3.4.1 Meta-analysis of SET on the VAS scores

Two studies assessed the VAS scores at different time points; therefore, a total of 13 VAS score comparisons were reported across 11 studies. A fixed effects model was used to integrate the results. SET significantly reduced the VAS score among the patients with LDH compared to the controls ($MD = -0.96$, 95% CI, -1.10 to -0.82 ; $p < 0.00001$, $I^2 = 23\%$) ([Figure 3](#)).

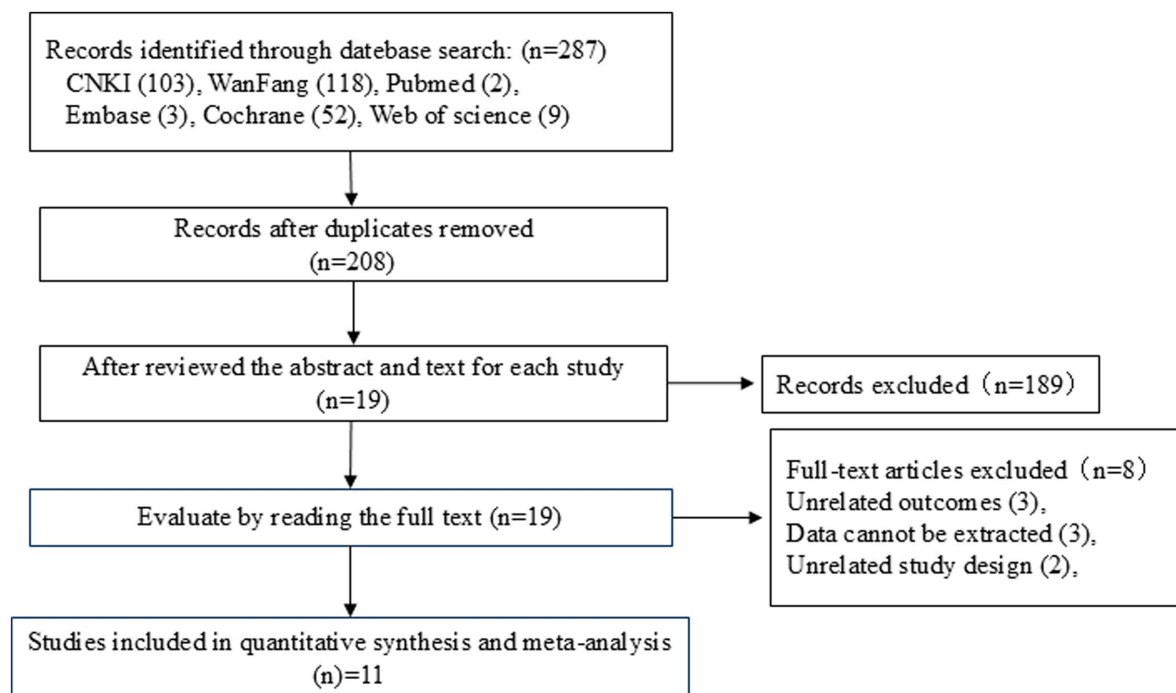


FIGURE 1
Literature screening flowchart.

TABLE 1 Basic characteristics of the included studies.

Reference	Age (Mean ± SD)	Sex (M/F)	Sample size	Intervention type	Intervention period	Outcome indicators	Follow- up
Yang et al. (29)	E: 58.6 ± 10.5	E: 17/23	E: 40	SET + McGill	2 weeks	①②③	Yes
	C: 55.0 ± 9.4	C: 11/29	C: 40				
Sun et al. (27)	E: 47.5 ± 11.3	E: 15/15	E: 30	SET + Rehabilitation	2 weeks	①	Yes
	C: 46.7 ± 10.9	C: 14/16	C: 30				
Du et al. (21)	E: 47.4 ± 14.6	E: 18/14	E: 32	SET + Breathing training	2 weeks	①②	Yes
	C: 48.2 ± 15.8	C: 17/15	C: 32				
Ding et al. (20)	E: 43.6 ± 8.8	E: 15/13	E: 28	SET + Tuina	4 weeks	①②	Yes
	C: 44.1 ± 8.5	C: 13/15	C: 28				
Li et al. (23)	E: 42.8 ± 11.1	E: 15/15	E: 30	SET + Massage	4 weeks	①②③	No
	C: 43.0 ± 10.8	C: 19/11	C: 30				
Li et al. (24)	E: 43.6 ± 10.2	E: 33/26	E: 59	SET + Massage	4 weeks	①②	No
	C: 43.1 ± 10.2	C: 31/28	C: 59				
Liang et al. (26)	NR	NR	E: 29	SET + Rehabilitation	4 weeks	①③	No
	NR	NR	C: 29				
Zhang et al. (30)	E: 53.0 ± 5.1	E: 16/14	E: 30	SET + Shockwave training	4 weeks	①③	Yes
	C: 52.9 ± 5.1	C: 15/15	C: 30				
Li et al. (25)	E: 46.7 ± 10.2	E: 17/15	E: 32	SET + Rehabilitation	4 weeks	①②	Yes
	C: 47.3 ± 9.2	C: 17/13	C: 30				
Khanzadeh et al. (22)	E: 37.2 ± 5.3	NR	E: 12	SET + core stability exercises	8 weeks	①	No
	C: 43.4 ± 8.6	NR	C: 13				
Xue et al. (28)	E: 56.5 ± 5.4	E: 91/59	E: 150	SET + pregabalin	4 weeks	①②③	No
	C: 56.4 ± 5.6	C: 89/61	C: 150				

E, experimental group; C, control group; M, male; F, female; NR, not reported; and SET, suspension exercise training.

3.4.2 Meta-analysis of SET on the JOA scores

Seven studies reported the JOA scores. A random effects model was used to integrate the results. SET significantly improved the JOA score among the patients with LDH compared to the controls (MD=3.29, 95% CI, 1.67 to 4.90; $p<0.0001$, $I^2=92\%$). Subgroup analyses of the JOA score based on intervention modality revealed that SET combined with traditional Chinese medicine (TCM) (MD=4.29, 95% CI, 2.73 to 5.86; $p<0.00001$, $I^2=80\%$) had better efficacy compared to SET combined with non-TCM (MD=0.96, 95% CI, 0.49 to 1.43; $p<0.0001$, $I^2=0\%$) and that intervention modality was the main source of heterogeneity in the JOA score among the patients with LDH (Figures 4, 5).

3.4.3 Meta-analysis of SET on the ODI scores

Five studies reported the ODI scores. A random effects model was used to integrate the results. SET significantly improved the ODI score among the patients with LDH compared to the controls

(MD=−5.41, 95% CI, −7.41 to −3.40, $p<0.00001$, $I^2=86\%$). Subgroup analyses based on the intervention period and intervention type did not reveal any sources of heterogeneity (Figure 6).

3.5 Sensitivity analysis

Heterogeneity for the two outcome indicators, the JOA score and ODI score, was high in this study. By removing one JOA score and one ODI score (whose treatments in this study were different from those in the other studies) through sensitivity analysis, the remaining combined results showed a significant decrease in heterogeneity ($I^2=83\%$ and $I^2=80\%$). However, there was still no statistically significant difference in the total combined results for the JOA scores (MD=3.73, 95% CI, 2.17 to 5.19, $p<0.00001$) and ODI scores (MD=−5.37, 95% CI, −8.33 to −2.42, $p<0.0004$), indicating that

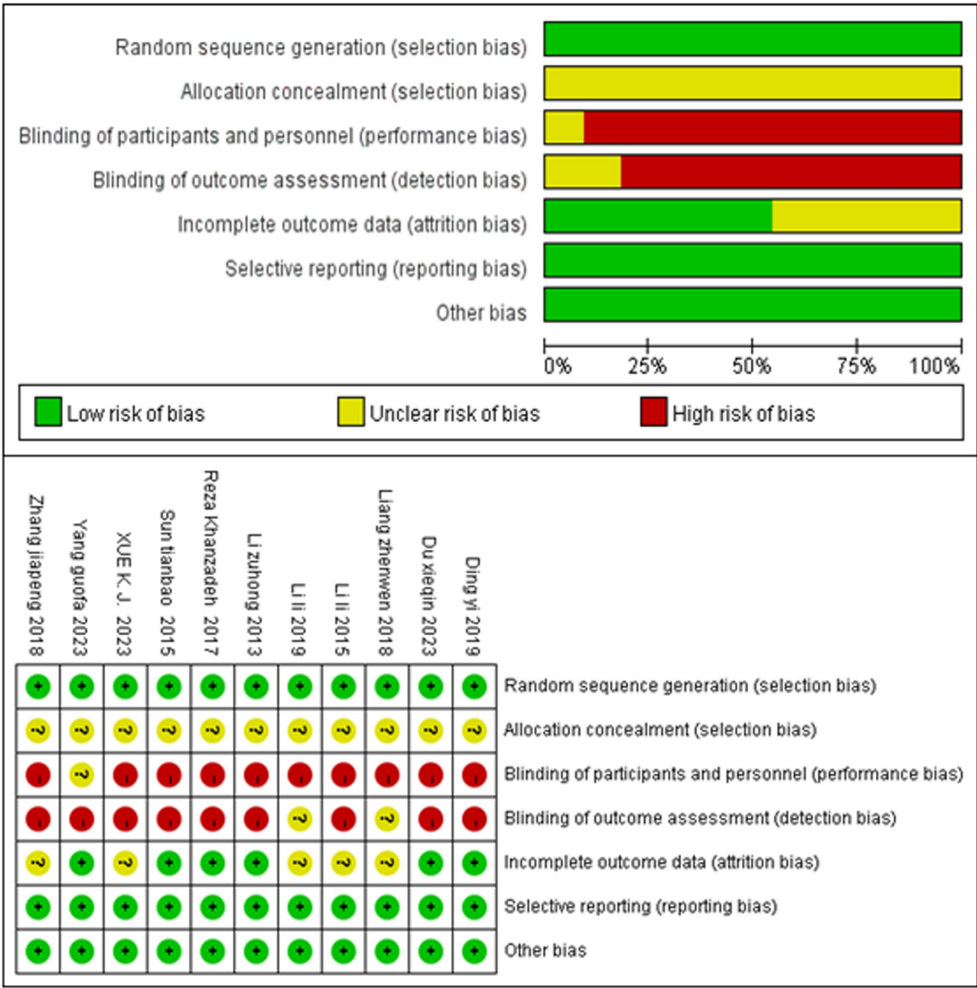


FIGURE 2
Quality evaluation results.

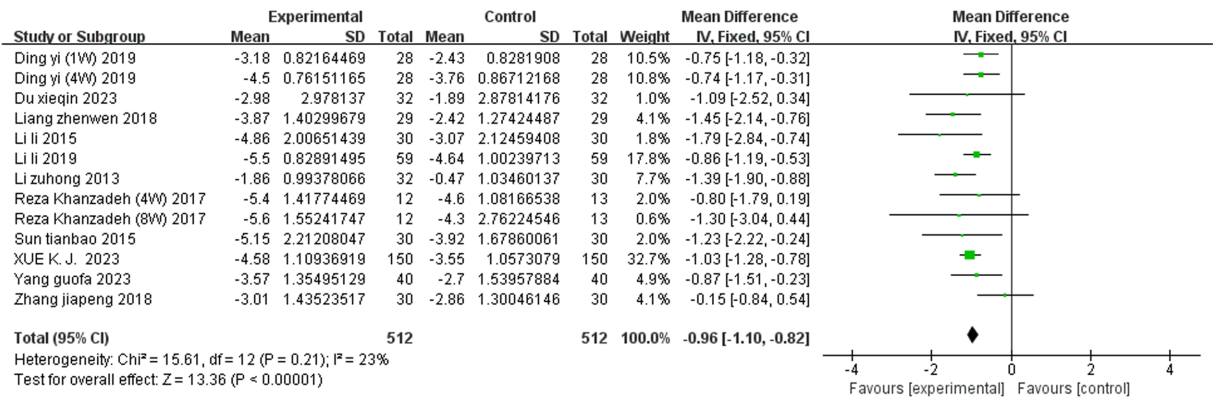


FIGURE 3
Meta-analysis of SET on the VAS score.

the findings of this study are relatively reliable. The detailed sensitivity analyses for the VAS score, JOA score, and ODI score are presented in [Supplementary Tables S2–S4](#) of the attachment, respectively.

3.6 Publication bias analysis

Funnel plots and Egger's asymmetry test were conducted for the VAS scores of the outcome indicators that included more than 10

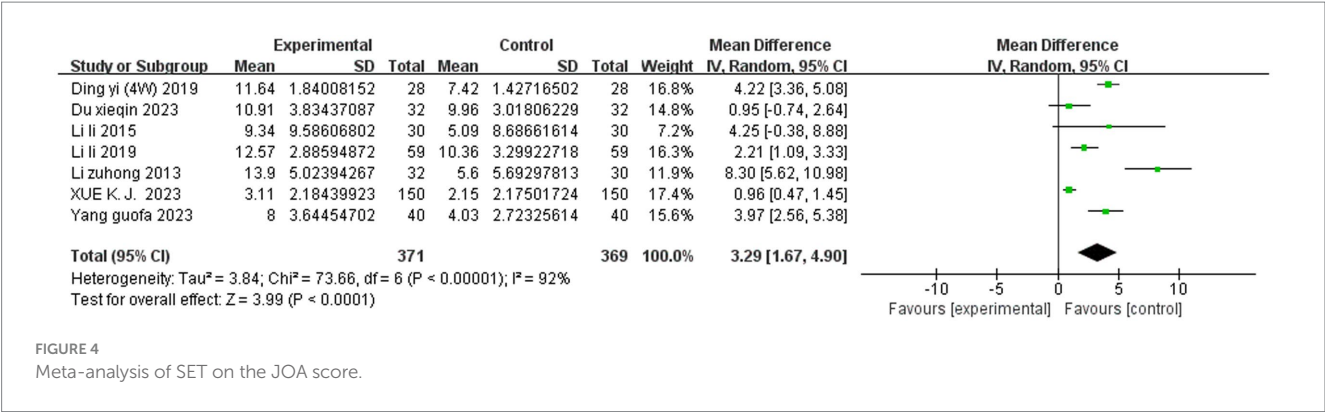


FIGURE 4
Meta-analysis of SET on the JOA score.

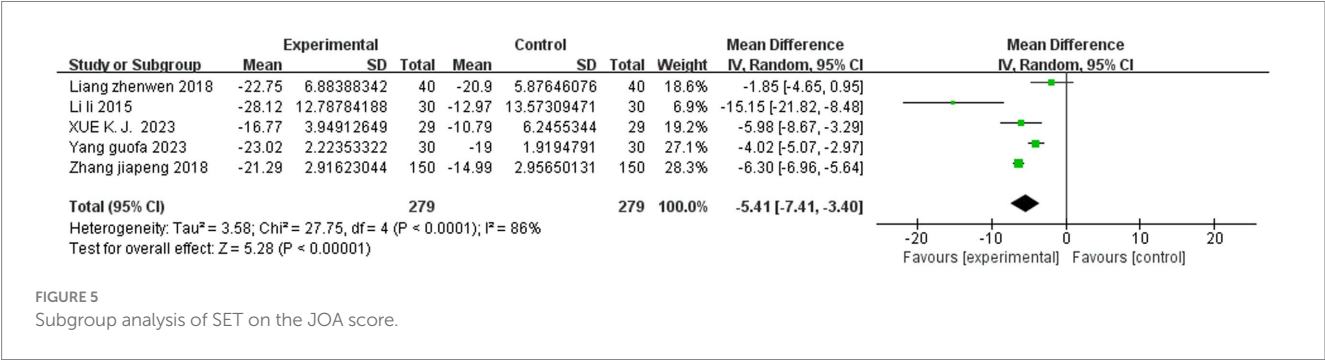


FIGURE 5
Subgroup analysis of SET on the JOA score.

studies. The results showed that the left and right sides were largely symmetrical, with the majority of the studies positioned in the upper middle. However, one study (30) fell outside the 95% confidence interval (dashed angled lines) (see Figure 7). The Egger's test indicated no publication bias ($p = 0.888$) (see Figure 8).

4 Discussion

To the best of our knowledge, this is the first meta-analysis that evaluates the efficacy of suspension exercise training in the treatment of LDH, focusing particularly on its effect on patients with lumbar disk herniation. A total of 11 studies involving 943 patients with lumbar disk herniation were included in this meta-analysis. The results indicated that suspension exercise training significantly improved the VAS, JOA, and ODI scores among the patients with LDH. Subgroup analyses revealed that the combined modality of suspension exercise training was the main source of heterogeneity in the JOA scores.

The VAS score (17) is a valid scoring method for measuring pain, represented on a straight line of 10 cm length, where one end signifies 0 for no pain and the other end signifies 10 for the most severe pain. This allows testers to assess the level of pain according to their own sensations; the lower the score, the lesser the pain, while the higher the score, the greater the pain. The results of this study showed that suspension exercise training significantly reduced the VAS scores among the patients with lumbar disk herniation, which is consistent with a previous study (31). However, unlike the previous study, which showed that suspension exercise training reduced the VAS score by 4.37 points, this overview showed that SET only reduced it by 0.96 points. This difference is mainly due to the lack of a control group in

the study as the VAS scores do not represent the mean difference between the experimental and control groups. Suspension exercise training can significantly reduce the VAS scores of patients with LDH for three main reasons. Firstly, suspension exercise training increases the lumbar intervertebral space by stretching the spinal column, which reduces the compression of lumbar disks on the nerves (32). Secondly, it can improve the microcirculation of lumbar soft tissues and accelerate the subsidence of inflammatory substances (33), thus reducing the production of pain factors. Finally, it can enhance the strength and coordination of the trunk muscle groups and improve the stability of the lumbar spine, thus reducing pain in patients with LDH (22).

The JOA score (18) is an effective scoring method for assessing the neurological functional status and daily living ability of patients with lumbar spine disease. It includes 25 scoring items, covering subjective symptoms, clinical symptoms, and daily living ability; the higher the score, the more obvious the functional improvement. The results of this overview showed that suspension exercise training significantly improved the JOA scores among the patients with lumbar disk herniation, which is consistent with a previous study (34). However, unlike the previous study, which showed that suspension exercise training improved the JOA scores by 5.28 points compared to traditional massage therapy, our study indicated that it only improved the scores by 3.29 points. We believe that this difference is mainly due to the intervention modality as suspension exercise training is not the only variable in the experimental and control groups. Suspension exercise training significantly improved the JOA scores among the patients with LDH. We believe that, on the one hand, suspension exercise training stimulates the neuromuscular coordination of contractions between the trunk muscles and major muscle groups of the body, thereby improving neuromuscular function (35). On the

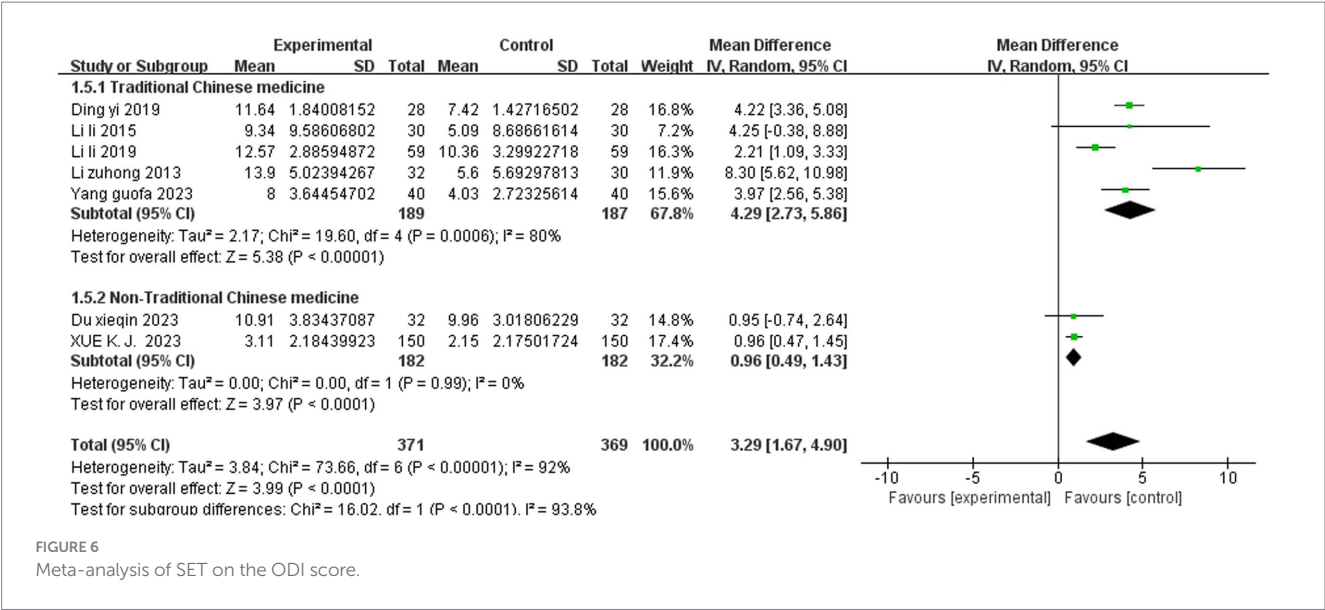


FIGURE 6
Meta-analysis of SET on the ODI score.

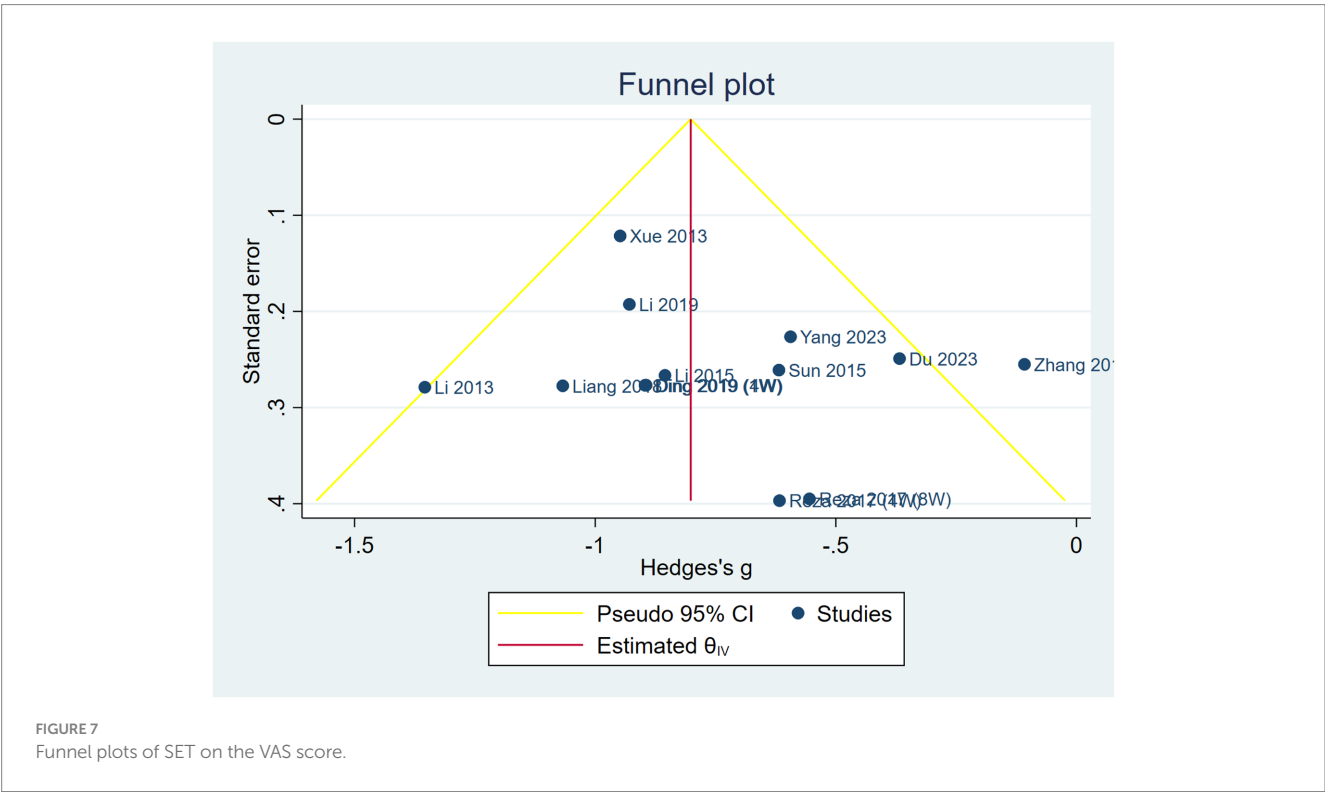


FIGURE 7
Funnel plots of SET on the VAS score.

other hand, suspension exercise training enhances the stability of the spine by strengthening the strength and coordination of the trunk muscle groups, thereby improving the body's balance, control, and stabilization during exercise (27). However, although suspension exercise training significantly improved the JOA scores among the patients with LDH, the study results showed a high degree of heterogeneity, which was significantly reduced after the deletion of one study (28). We believe this may be attributed to the intervention of suspension exercise training combined with pharmacotherapy. The subgroup analyses showed that suspension exercise training combined with traditional Chinese medicine had a better effect on improving the JOA scores among the patients with LDH. Therefore, future studies need to further validate the therapeutic effects of suspension exercise

training combined with traditional Chinese medicine to determine the optimal combination modality.

The ODI score (19) is a validated scale commonly used to evaluate dysfunction related to lower back pain. There are a total of 10 scoring components, covering a variety of aspects such as pain level, daily living ability, walking, and standing, with higher scores indicating more severe dysfunction. The results of this study showed that suspension exercise training significantly reduced the ODI scores among the patients with LDH, which is consistent with a previous study (36). This is mainly due to the fact that suspension training addresses gravity with the help of adjustable slings and ropes, placing the patient on an unstable plane. This increases the stimulation of proprioceptive input in the lumbar core stabilizing

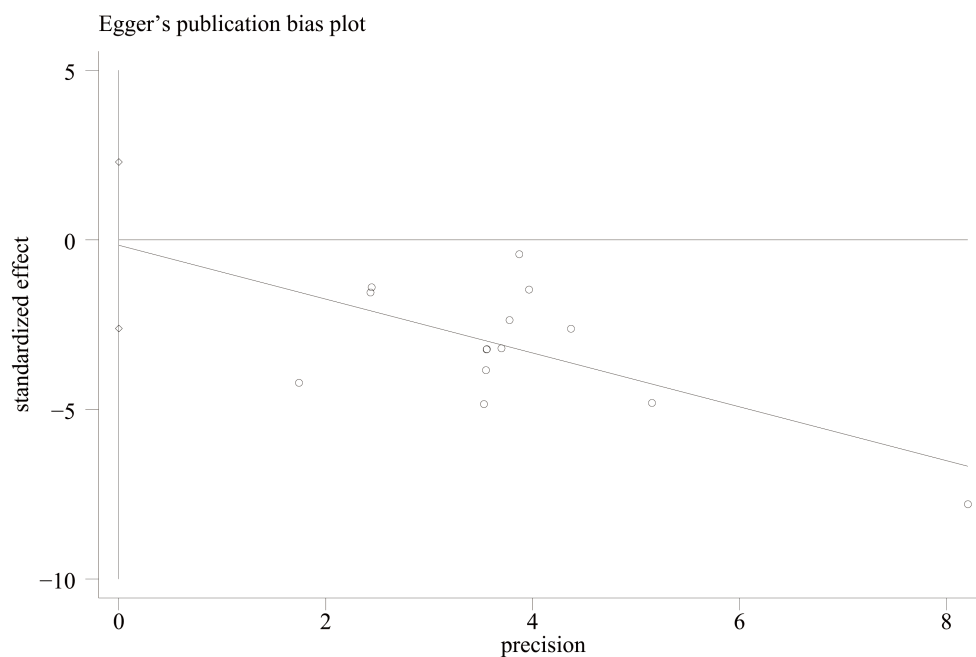


FIGURE 8
Egger's publication bias plot for the VAS score.

muscle groups through safe, stepwise training, activates and recruits more motor units to enhance the muscle strength of target muscle groups, rebuilds the normal muscle movement pattern, and strengthens the stability of the spine, ultimately improving lumbar spine function (26) and reducing the ODI scores of patients with LDH. However, the results of the study showed a high degree of heterogeneity, which was significantly reduced after the deletion of one study (28), although there was no valid reason to delete this study. The subgroup analyses of the intervention duration and treatment modalities did not reveal a source of heterogeneity. We believe that the combined modality of suspension exercise training, the location of lumbar disk herniation, and the population affected by it might have been the sources of heterogeneity, which need to be further investigated in future studies. On the other hand, only five studies were included in the ODI scores of this review, and the small number of studies might have contributed to the high heterogeneity.

5 Limitations

This study has the following three limitations. First, the number of studies included and their reliability need further improvement. Second, the VAS, JOA, and ODI scores rely on subjective evaluation scales. Finally, the meta-analyses of the JOA and ODI scores showed high heterogeneity.

6 Conclusion

In conclusion, suspension exercise training significantly improved the VAS, JOA, and ODI scores of the patients with lumbar disk

herniation; however, there was a high degree of heterogeneity in the JOA and ODI scores. Further validation is needed in the future for different populations with lumbar disk herniation, the specific locations of its occurrence, and the combined modalities of suspension exercise training.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#), further inquiries can be directed to the corresponding author.

Author contributions

YL: Methodology, Writing – original draft, Conceptualization. SH: Data curation, Writing – review & editing. XZ: Software, Writing – review & editing. HL: Data curation, Writing – review & editing. WL: Supervision, Visualization, Writing – review & editing. ZZ: Supervision, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2024.1455505/full#supplementary-material>

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DBS in the restoration of motor functional recovery following spinal cord injury

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The landscape of therapeutic deep brain stimulation (DBS) for locomotor function recovery is rapidly evolving. This review provides an overview of electrical neuromodulation effects on spinal cord injury (SCI), focusing on DBS for motor functional recovery in human and animal models. We highlight research providing insight into underlying cellular and molecular mechanisms. A literature review via Web of Science and PubMed databases from 1990 to May 29, 2024, reveals a growing body of evidence for therapeutic DBS in SCI recovery. Advances in techniques like optogenetics and whole-brain tractogram have helped elucidate DBS mechanisms. Neuronal targets sites for SCI functional recovery include the mesencephalic locomotor region (MLR), cuneiform nucleus (CNF), and nucleus raphe magnus (NRG), with pedunculo pontine nucleus (PPN), periaqueductal gray (PAG), and nucleus ventroposterolateral thalami (VPL) for post-injury functional recovery treatment. Radiologically guided DBS optimization and combination therapy with classical rehabilitation have become an effective therapeutic method, though ongoing interventional trials are needed to enhance understanding and validate DBS efficacy in SCI. On the pre-clinical front, standardization of pre-clinical approaches are essential to enhance the quality of evidence on DBS safety and efficacy. Mapping brain targets and optimizing DBS protocols, aided by combined DBS and medical imaging, are critical endeavors. Overall, DBS holds promise for neurological and functional recovery after SCI, akin to other electrical stimulation approaches.

KEYWORDS

deep brain stimulation, neural circuits, neuromodulation, neuroplasticity, spinal cord injury, motor function

Introduction

The standard of care for spinal cord injury patients consists of acute surgical intervention and intensive post-acute rehabilitation. Despite the positive recovery of sensorimotor functions achieved by these methods, complete functional recovery is largely limited (1). There is very low evidence that these intervention improves ASIA motor score (AMS) in the short term (2), moreover, the anticipated undesirable effects include any major complication, surgical device-related complications, pressure ulcer, sepsis secondary to systemic infection, neurological deterioration, need for tracheostomy, and cardiopulmonary dysfunction (3). Therefore, finding a more effective and safe treatment plan is the top priority. The approach of electrical stimulation of the spinal cord to enhance

functional recovery has yielded promising results. This review aims to provide an overview of the neural circuitry remodeling mechanisms of deep brain stimulation (DBS) after spinal cord injury, which may contribute to the improvement of motor function. DBS has been successfully used in the treatment of various movement disorders for years (4). The body of literature regarding DBS for SCI recovery has steadily increased in the past decade. In fact, DBS is currently also being applied post-SCI with promising results (5). However, the majority of research on DBS for SCI have focused on its efficiency on SCI-related neuropathic pain, while very few have attempted to ascertain the effects of DBS on motor functional recovery after SCI. In addition, some intrinsic mechanisms involved in the beneficial effects of DBS have been identified, including neuronal circuit remodeling, and potential alterations in intracellular signaling induced by DBS (6). Pre-clinical models have shed important light on mechanisms and best approaches, while researchers continue to synthesize and interpret outcomes from heterogeneous applications and populations. By far, radiologically-guided DBS has demonstrated the greatest improvement in patient outcomes, in addition to allowing the refinement of functional targets as the body of literature evolves (Figure 1).

Search strategy

The articles used in this review of DBS for SCI treatment were retrieved by replicating the search terms of Vanegas et al. (7). A narrative review of the literature was performed using the keywords “DBS,” “Spinal Cord injury,” and “motor function,” via Web of Science, Google Scholar and PubMed databases. The search strategy and selection criteria utilized keywords/terms: deep brain stimulation (MeSH Terms), neural circuits (MeSH Terms), Spinal cord injuries (MeSH Terms), neuromodulation (MeSH Terms), neuroplasticity (MeSH Terms), motor function (MeSH Terms).

The inclusion criteria: Studies providing preclinical and clinical motor function results after DBS treatment in SCI models. For animal study, retrospective or prospective clinical studies were included. Papers had to be published in English between January 1990 to May 29, 2024.

The exclusion criteria: Reviews, meta-analyses, and those written in a non-English language, and studies concerning DBS treatment SCI related- pain. Other articles for whom the full text could not be retrieved were excluded.

Selection Process: The detailed study selection process is visually represented in Figure 2 within the PRISMA flowchart (8). Ultimately, we included 79 articles in our review. The protocol was registered with PROSPERO (registration ID: 598390).

Quality assessment: The assessment of the methodological quality of individual studies was conducted independently by two researchers (WYL and WY) according to a checklist designed by Van (9).

Post-SCI neuronal circuit remodeling

After SCI, local circuits within the spinal cord may partially or completely lose their cortical spinal motor inputs. Complex corticospinal circuit remodeling ensues, demonstrating automaticity and spontaneous plasticity (10). While some spontaneous plasticity occurs to benefit the regeneration of the corticospinal tract, off-target re-wiring can be detrimental to recovery. Circuit remodeling facilitating functional recovery mainly operates via supraspinal axon re-growth to form compensatory circuits. Target selection of these axons is critical, with various competing relay neurons and axon guidance factors at play. Ultimately, evidence suggests this modulation is activity-dependent (11), and can thus be therapeutically utilized to improve motor function after SCI. Indeed, this has been the premise of neurorehabilitation and locomotor training for years (12, 13).

In the past decade, many strategies to facilitate neuromodulation after SCI have been developed, including stem cell implantation, epidural stimulation (ES) and DBS. In this review, we will focus on the body of evidence for DBS as a tool for neuromodulation, circuit remodeling, and functional recovery after SCI.

Premise for neuromodulation via DBS in SCI

The study of high-frequency DBS for therapeutic purposes was pioneered decades ago. Since then, elegant hypotheses have been elaborated to explain the most complex aspect of DBS—its dynamic stimulatory properties (14). The synchronized parallel forebrain hypothesis (an extension of the rudimentary centrencephalic system initiated by Wilder Penfield) proposes that ablation results from high-frequency DBS when it targets synchronous neurons and stimulation when it targets asynchronous neurons. Since, the focus in DBS research has largely remained to target and activate residual neural pathways in such a way to activate locomotion (e.g., via central pattern generator networks), though use of DBS for stereotactic ablation has gained traction for the treatment of movement disorders (15). Recently, implantable electrical stimulation modalities have been increasingly used in combination with high-throughput computer simulators, which rapidly record circuit feedback to refine spatiotemporal selectivity and improve functional features (16).

The FDA approved DBS for use in Parkinson's Disease (PD) patients in 2015 (17). Since, DBS has been trialed in human patients with largely positive outcomes (18, 19) observed from stimulation of the subthalamic nucleus (STN) and globus pallidus interna (GPi), including stable and longitudinal motor function improvement. More studies have since substantiated the efficacy of DBS as a surgical intervention for other tremor-based disorders (20, 21).

Deep brain stimulation typically consists of intracranial electrodes implanted surgically and connected to a subcutaneous impulse generator. The procedure has been generally well-tolerated (22). This finding was reported in a meta-analysis of randomized controlled PD trials, and may not translate to DBS for SCI patients. Despite any reservation, the use of DBS as a neuromodulatory therapeutic only continued to expand, recently gaining popularity as a therapeutic for diverse psychiatric disorders (23). Its efficacy in SCI patients appears to be variable and correlated with target region and stimulation parameters (24). As such, identifying and better understanding these

Abbreviations: SCI, Spinal cord injury; ES, epidural stimulation; DBS, Deep Brain Stimulation; STN, subthalamic nucleus; CST, Corticospinal Tract; GPi, globus pallidus interna; PAG, periaqueductal gray; CnF, cuneiform nucleus; RS, reticulospinal tract; CPGs, central pattern generators; RuS, rubrospinal tract.

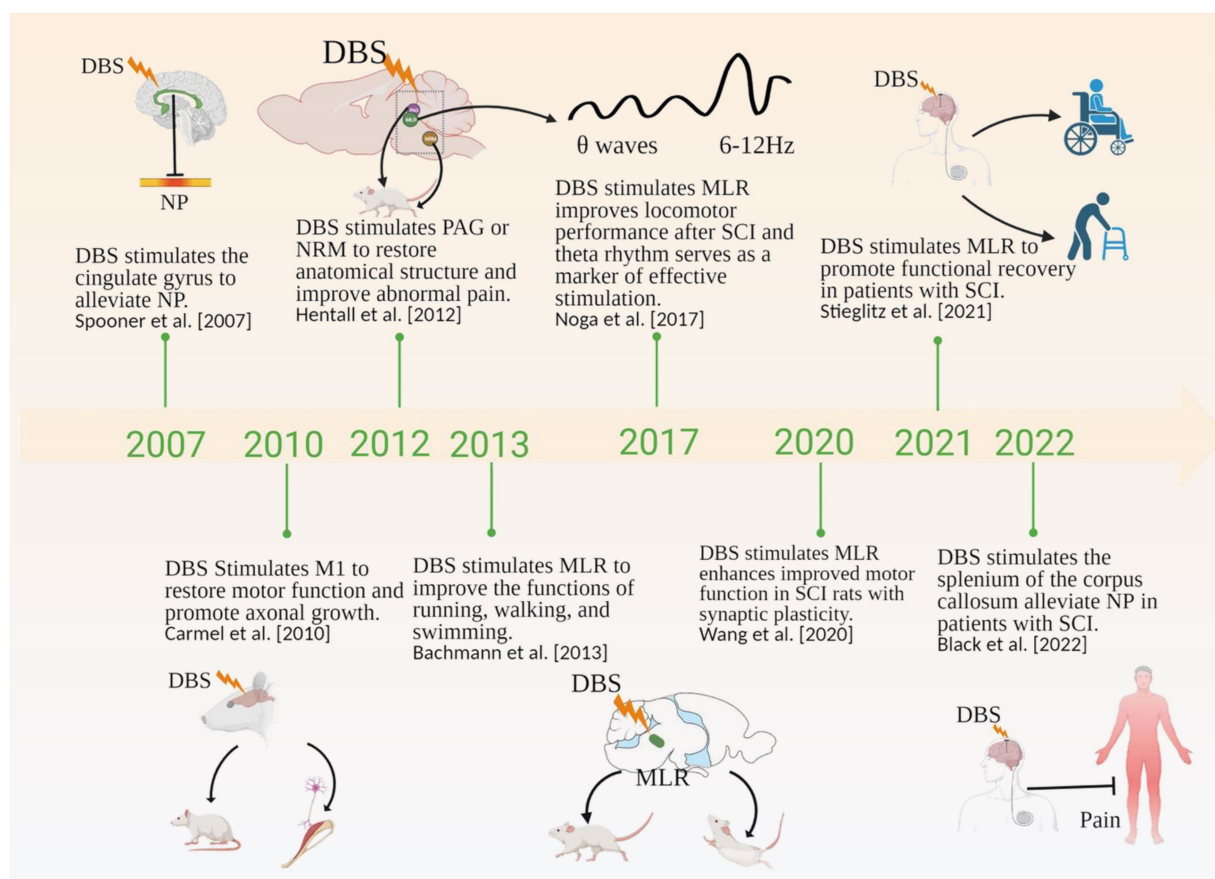


FIGURE 1

Timeline showing the role of DBS in SCI in the literature. NP, Neuropathic Pain; PAG, periaqueductal gray; NRM, nucleus raphe magnus; MLR, mesencephalic locomotor region. Created with [BioRender.com](https://www.biorender.com).

targets and their role in recovery mechanisms is crucial for optimization of DBS. For example, the brainstem has become a therapeutic target of SCI due to its ability to coordinate locomotor systems via the integration of sensory, cognitive, endocrine, autonomic, and musculoskeletal systems in animal models (25). It additionally remains crucial to optimize techniques and stimulation parameters to achieve improved and sustained benefits while minimizing safety risks (26). Some advantages of DBS include its rather broad applicability to neurosystemic targets in addition to its dual hemispheric tolerability and customizability from the electrical source.

Effects of DBS on motor function after SCI

Early animal studies of direct activation of the corticospinal tract through DBS of the internal capsule demonstrated increased axonal outgrowth of the CST in non-human primates (27). DBS selectively activates axons specific orientations by modifying the stimulation configuration, and selectively stimulating axons, substantially enhancing the potential clinical outcomes of DBS in SCI patients (28). Additional research has provided comparable insights into the effectiveness of DBS in rodent models of SCI subsequent to targeted

activation of subcortical locomotor regions. Other studies have similarly shed light on the efficacy of DBS in enhancing motor function in rat SCI models following specific activation of subcortical locomotor areas (25, 29). Bachmann and colleagues demonstrated that an MLR stimulation paradigm was sufficient to recover locomotor strength in just 4 weeks, re-establishing near pre-lesion walking capacity of injured rats (25). Hentall and colleagues reported that stimulation of the raphe magnus or periaqueductal gray (PAG) in lesioned rats produced sustained improvements in locomotor performance and increased axon myelination and serotonergic terminals, noting that window of DBS treatment produced variable recovery (29). Other studies have reported functional improvements in hindlimb motor function (30) in response to stimulation, while others targeting neuromodulation of CnF observed accelerated forelimb locomotor recover and late-onset hindlimb activation and improved walking ability within 5 weeks (31). Several studies have revealed its application in improving motor function by targeting the subcortical motor area for stimulation in the animal SCI model (25). Differential functional recovery response across studies is likely due to degree of spared fibers within the injured spinal cord (variability of lesion protocol), target area stimulation, and DBS parameters (Figure 3).

To date, whether DBS could promote recovery of voluntary locomotor ability has not been clarified in humans. A current trial

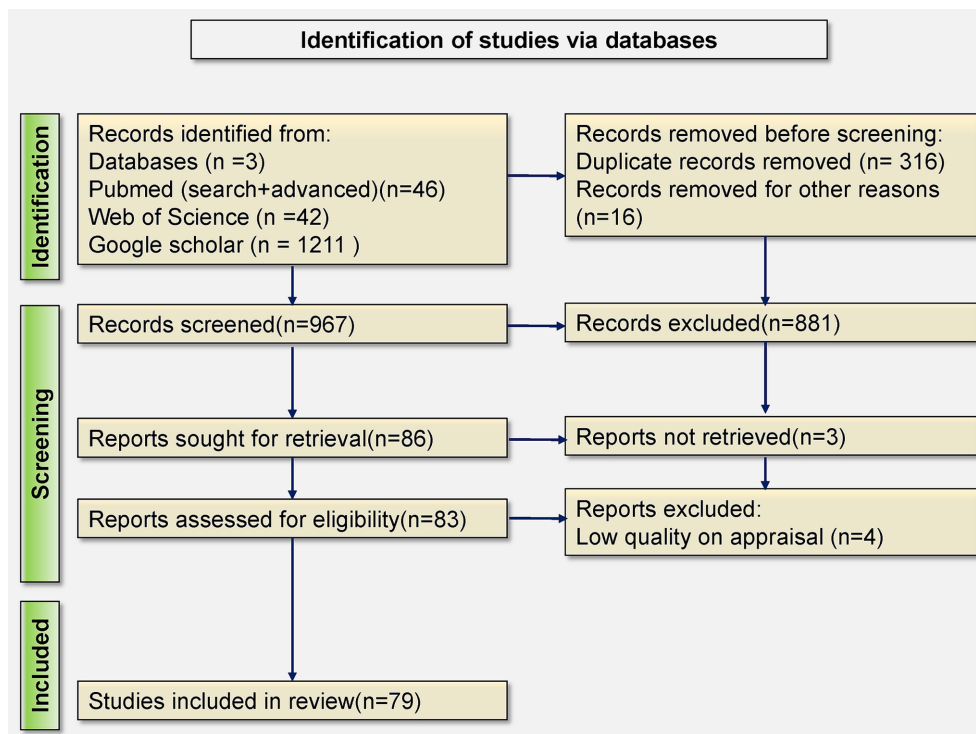


FIGURE 2
PRISMA flowchart depicting article selection.

(NCT03053791) is underway for non-ambulatory SCI patients experiencing subchronic and chronic SCI. Based on experience gained from the first study participant in this clinical trial, the motor function of the SCI patients is most likely to benefit from MLR- DBS (5), which provides preliminary clinical evidence for the DBS in the restoration of motor functional recovery following SCI. The main endpoint for this human trial is enhanced locomotor recovery in chronic SCI patients undergoing intense neurorehabilitation (32). Nevertheless, few clinics evidence for the efficacy of DBS in the management motor functional following SCI. Instead, the vast majority evidence of SCI-related neuropathic pain patients who are the most likely to benefit from the DBS.

DBS regulation of cortical circuits

The descending reticulospinal tract (RS) is prime conveyor or locomotor commands from the brain to intraneuronal circuits. After SCI, the number of spared fibers is typically insufficient for appropriate control of sublesion locomotor circuits (5). Some of the compromised locomotor circuits include central pattern generators (CPGs), responsible for alternating motion and syncing. There is some evidence that with training, electrical stimulation can re-activate these CPGs (33, 34). Importantly, there is evidence that lumbosacral CPGs can respond to external electric stimulation, even in the absence of sub-lesion response to supraspinal inputs (which has important implications for complete SCI patients) (35). Due to the input source of reticulospinal fibers, the MLR has become a major target of neuromodulation approaches in SCI treatment. A caveat of

MLR-applied DBS for the treatment of SCI is the required residual reticulospinal fibers, which are only observed in incomplete SCI cases. Fortunately, the estimated rate of incomplete human SCIs outnumbers complete SCIs about 2:1 (36).

The rubrospinal tract (RuS) has been implicated in the recovery of cortical-dependent locomotion, including walking, climbing and swimming (37). DBS of the subcortical-cerebellar pathway demonstrated recruitment of the cortico-basal ganglia circuit during both resting state and voluntary movement (38).

By creating a whole-brain tractogram, the reconstruction of CST, pallidothalamic (PT), and cerebellothalamic (CBT) pathways are directly relevant to DBS activates particular axonal pathways (39, 40). Additionally, DBS can increase the functional connectivity of the motor and premotor cortex, enhancing motor coordination and response to mechanical stimulation.

Sophisticated studies have revealed that glutamatergic MLR neuron activation is sufficient to initiate and regulate locomotor acceleration (41, 42). Similar observations have been reported on the function of glutamatergic CnF neurons during the initiation and regulation of gait (43). Conversely, glutamatergic PPN neurons may play an inhibitory role in locomotion, regulating variable pre-motor properties such as motor tone (43). It has been proposed that one of the ways MLR stimulation may be rehabilitative to the injured spinal cord is by increasing synaptic plasticity among surviving reticulospinal pathways (44) (Figure 4). Indeed, many neuromodulatory approaches have been adapted to leverage the spontaneous compensatory sprouting of proximal corticospinal fibers to promote functional reorganization of spinal sensorimotor networks (45) in ways akin to the activity-dependent plasticity that assists in functional recovery

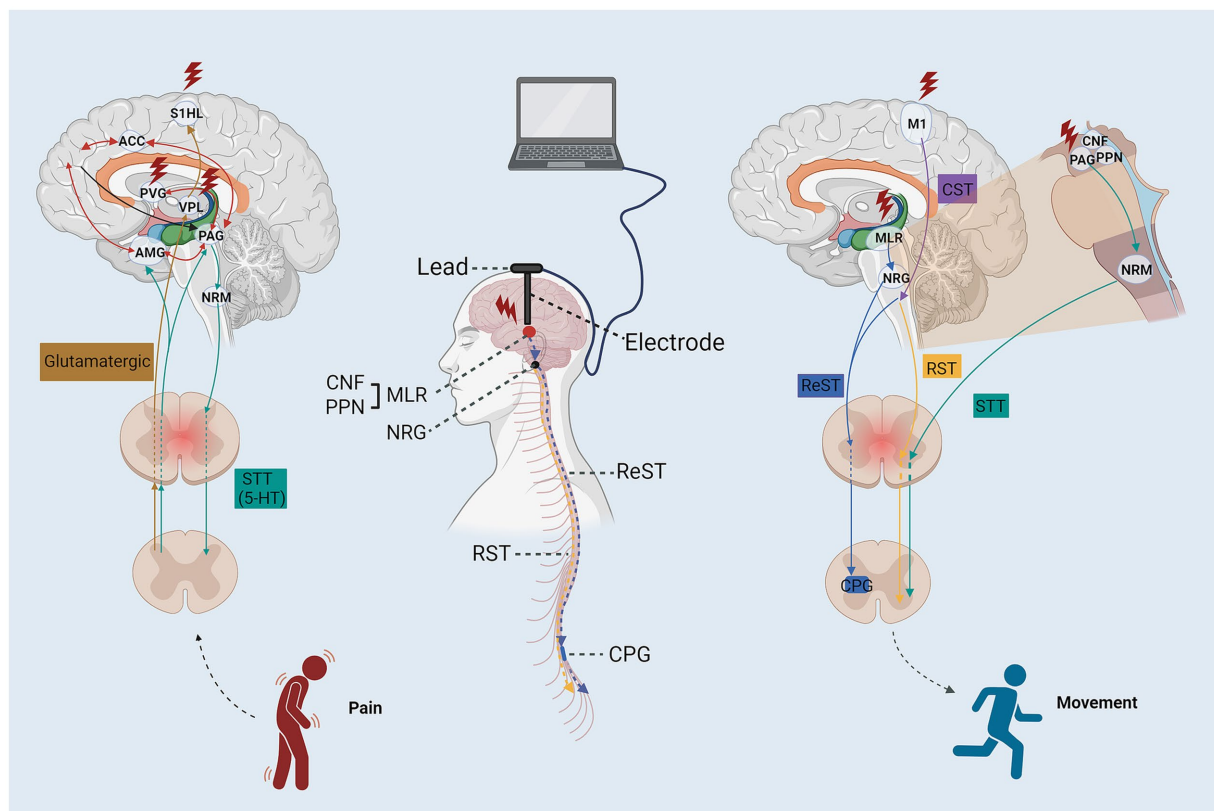


FIGURE 3

The schematic diagram of the stimulation targets and neural circuit for DBS enhance motor and sensory function after SCI. ACC, anterior cingulate cortex; ReST, reticulospinal tract; STT, spinothalamic tract; RST, rubrospinal tract; CST, corticospinal tract; AMG, amygdaloid nucleus; PFC, prefrontal cortex; PVG, periventricular gray; S1HL, somatosensory cortex hindlimb cortex; VPL, nucleus ventroposterolateral thalami; PAG, periaqueductal gray; NRM, nucleus raphe magnus; PPN, pedunculopontine nucleus; NRG, gigantocellular reticular nucleus; CPG, central pattern generators.

during post-injury rehabilitation (46). Raphe magnus neuron stimulation via inputs from the more accessible periaqueductal gray (PAG) have been safely accessed for drug-refractory pain treatment by DBS in human (47). In a rat model of SCI, 4–7 day stimulation protocol produced motor recovery and myelination (29). However, to-date, the large majority of DBS studies targeting the PAG have focused on the treatment of post-SCI functional recovery (24). Overall, DBS can enhance corticospinal circuit remodelling and elicit complex, meaningful locomotor patterns by utilizing preserved complex spinal cord circuits following SCI (43). SCI patients with preserved spinal cord circuit fibers may have a beneficial outcome from DBS treatment, which may potentially enhance their daily functioning.

Other circuits to be investigated more deeply include those that negatively affect functional recovery after SCI. For example, long ascending propriospinal neurons that regulate central pattern generator (CPG) to contribute to left–right coordination of hindlimbs have been shown to negatively impact the recovery of hindlimb locomotor function in a rat SCI model (48). Recently, the idea of silent synapse (AMPA-deficient, glutamatergic post-synapse contacts) remodeling after SCI has also been proposed, prompting new questions about how neuromodulatory approaches may be applied to normalize these in the corticospinal motor circuitry post injury (45). Many SCI patients experience motor spasticity that

negatively impacts quality of life. While no DBS studies have investigated its effect on post-SCI spasticity, recent meta-analysis and systematic review has outlined that repetitive transcranial magnetic stimulation (rTMS) significantly reduced spasticity in a population of multiple sclerosis patients (49). More research on the neuromodulation of targets responsible for voluntary muscle contraction (e.g., global pallidus internus) is needed in the SCI population.

Cellular and molecular mechanisms of DBS neuromodulation

Toward an improved understanding of the molecular mechanisms conferring the therapeutic and neuroadaptive effects of deep brain stimulation, one study has reported that DBS-derived synaptic plasticity is mediated in part by elevations in brain derived neurotrophic factor (BDNF) and downstream synaptic proteins (30). Other models of electrical stimulation have similarly observed upregulated BDNF (50, 51) DBS also elevates the BDNF receptor tropomyosin-related kinase B (TrkB), p70 ribosomal S6 protein kinase, and protein kinase B (30). This pathway is corroborated by other electrical stimulation paradigms including peripheral nerve stimulation (52). The BDNF/TrkB pathway is thought to activate

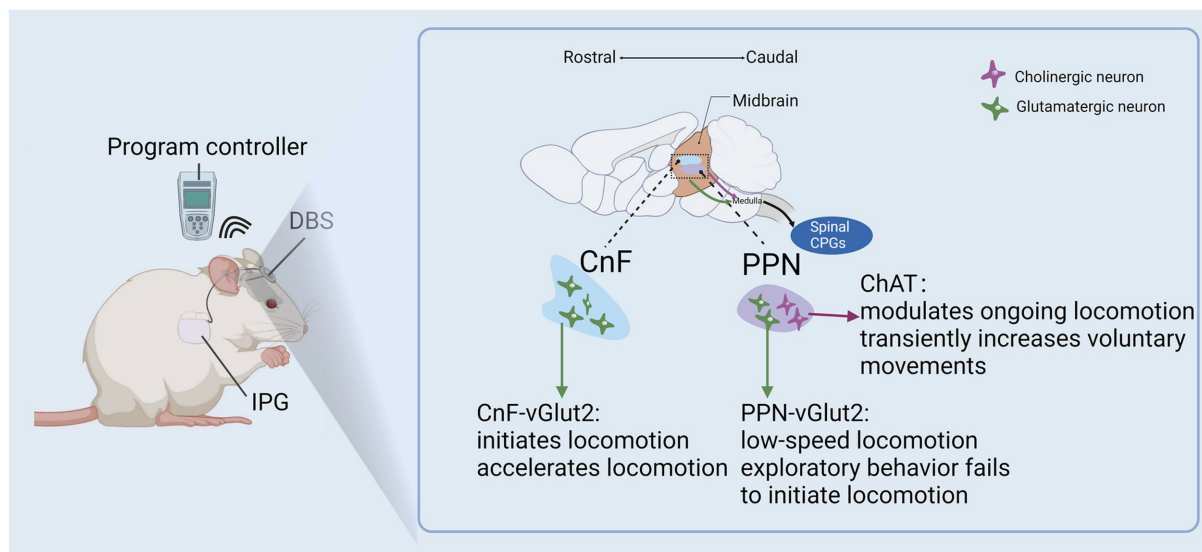


FIGURE 4
DBS of the MLR improve remodeling of cortical circuits after SCI.

neuroprotective, neuroplasticity, and pro-regenerative signals to aid in functional remodeling after SCI (53).

Improved understanding of the anatomical contributors to locomotor initiation and control come from optogenetic studies revealing the distinct physiological and functional subpopulations. For example, the glutamatergic CnF population were found to initiate short latency locomotion (41, 43) while ventrally-adjacent glutamatergic PPN neurons are thought to either not contribute to locomotor initiation or exploratory locomotion only (41). A study of the MLR in freely moving micropigs has provided electrical characterization including off-target effects of brainstem cardiovascular centers (54). This study corroborated the role of DBS on locomotor initiation and frequency-dependent speed regulation as well as (54). There are no clear boundaries for the sub-regions of the MLR, particularly in higher-order vertebrates. The PPN is largely characterized by its neuronal subpopulations, including cholinergic, glutamatergic, and GABAergic neurons. While optogenetic studies have proposed cholinergic PPN neurons play a role in locomotion (41), other studies have reported little to no effect on locomotion or speed (55).

Evidence from electrical stimulation studies has shown that while functional improvement is achieved with external stimulation after SCI, long-lasting functional improvements can be observed chronically, in the absence of the external signal (37, 56). This indicates that sustained neuroplasticity occurs after therapeutic intervention to support long-term recovery. Indeed, epidural electrical stimulation (EES) paradigms have demonstrated robust and specific transcriptional and neurotransmitter changes to subsets of specialized interneurons in response to EES (57). In reality, the mechanisms of DBS on SCI remodeling are likely diverse and cumulative, including proximal and circuit-wide electrical and chemical effects to modulate activity, plasticity, and anatomical re-organization over time (58). As technical advances allow for more sophisticated experiments, we expect to increasingly delineate the

contributory mechanisms and functional circuits that make-up the pathogenesis of SCI (Figure 5).

Trajectory and protocol optimization of DBS for SCI

One of the remaining challenges of DBS for neuromodulation of SCI is identifying precise and effective brain regions to achieve maximal therapeutic efficacy and minimizing off-target effects. This type of trajectory planning is required in part due to the poor characterization of many regions of the brain related to locomotor regulation in humans (59). Mapping anatomical substrates with their maximal therapeutic response can help build predictive tools for clinical decision-making and is a step toward fully personalized application of DBS.

One such approach is probabilistic stimulation maps (PSM) derived from retrospective DBS datasets. These maps are based on activation volumes observed by medical imaging across heterogeneous populations. In short, using MRI imaging and activation volume modelling, PSMs were created and described in terms of their interactions with surrounding anatomical structures, defining areas of above-mean and below-mean response for each patient cohort. However, the major limitations of current approaches to PSMs is the accuracy of predefined DBS targets. PSMs predictive capability was not high and likely reflects both technical limitations of the mapping technique as well as the merging of numerous patient data on MRI models, which failed to consider each patient's individual neuroanatomical location and variations after SCI. Consequently, PSMs alone are currently insufficient as a robust and consistent predictor of clinical outcome (60). One center collected 15 years' worth of data from 482 patients, noting high correlations between PSMs and actual patient activation volumes (61). Another group created a machine learning model to predict optimal vs. non-optimal DBS parameters in a prospective cohort of 67 PD patients who underwent fMRI-observed

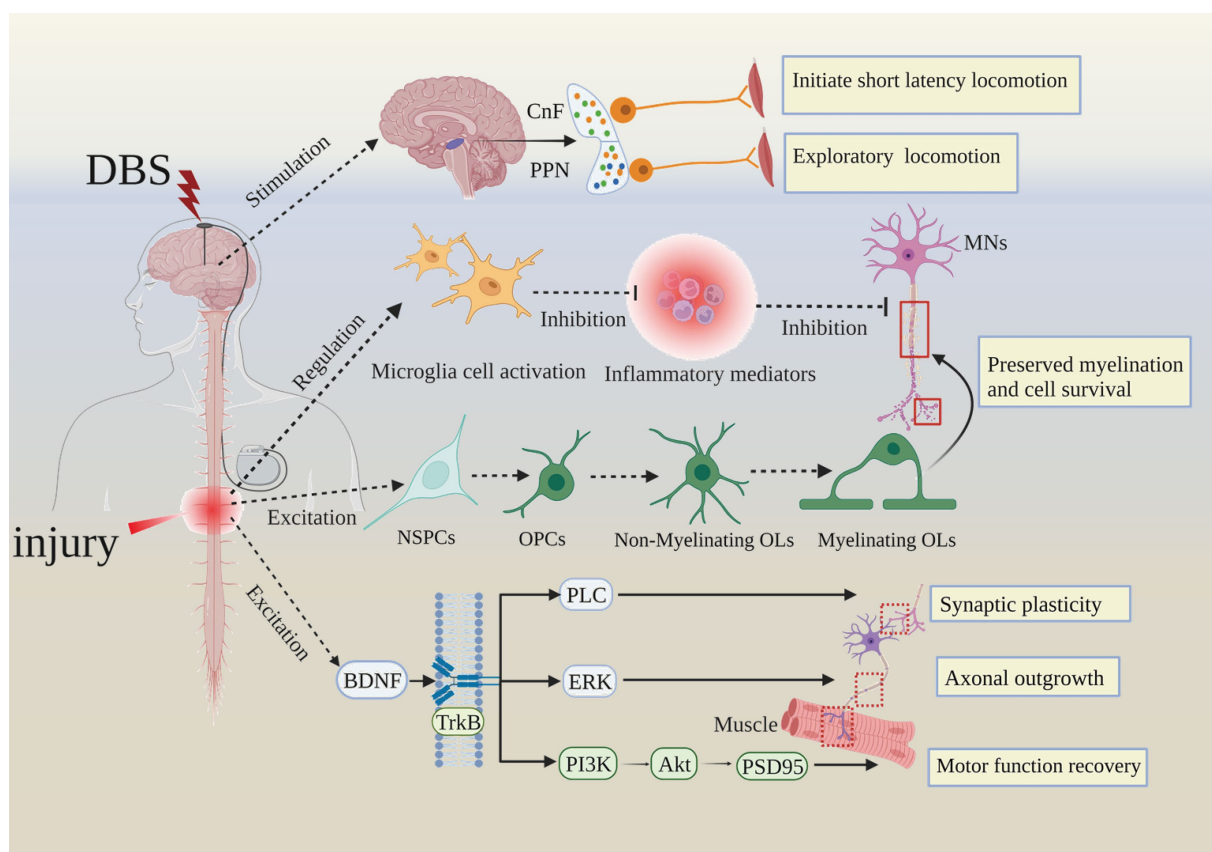


FIGURE 5

Summarizing the cellular and molecular mechanisms of DBS improves SCI prognosis. Akt, Protein Kinase B; CnF, cuneiform nucleus; MNs, motor neurons; NSPCs, neural stem/progenitor cells; OPCs, Oligodendrocyte precursor cells; OLs, oligodendrocytes; PLC, phospholipase C; ERK, extracellular regulated protein kinases; PI3K, Phosphoinositide-3 kinase; PSD95, postsynaptic density-95.

stimulation. The predictive response maps generated were 88% accurate and maintained their topographic patterns across subtherapeutic and suprathreshold stimulation parameters (62). More mapping efforts are reasonably expected. One important consideration as these trajectory planning strategies move forth are the different analytical methods being utilized, as these have substantial variability even within the same datasets (60). Although PSM accuracy needs to be thoroughly examined, it may enhance the comprehension of the effects of DBS and have potential applications for DBS targets in the treatment of SCI.

Electrophysiological mapping of MLR has been most notably investigated for the treatment of movement disorders with DBS. Some investigations have used local field potential monitoring across subregions of the MLR to examine the effectiveness of these targets in animal models. For example, voluntary locomotion in normal rats produces synchronized theta oscillations (6–12 Hz) in the MLR in intact rats and other regulatory regions of locomotor control. Interestingly, these theta oscillations persist after SCI in the MLR and may be useful in target planning during therapeutic DBS (63). On the other hand, the optogenetic stimulation of the PPN subregion at ~40 Hz has been shown to reliably induce locomotion in animals (64). One study used a combination of electromyographic recording, genetic manipulation, and anatomical analysis in an animal SCI model, reporting that glutamatergic neurons within the CnF improve

motor performance in the hindlimb muscles while glutamatergic PPN neurons inhibit locomotion when activated (65). Those findings are consistent with previous reports of DBS of the CnF, which produced enhanced motor drive in rats with incomplete SCI, allowing high-intensity locomotor training after injury (44). Finally, a micropip model of radiologically-guided DBS found that functional stimulation of the MLR was based on deliberate targeting of a PPN cholinergic population and a CnF cluster dorsal to that (54). Thus, as more detailed evidence becomes available, investigators must work toward an increasingly defined “map” of the MLR for DBS targeting.

Finally, it remains important to optimize lead implantation and stimulation protocols to maximize efficacy and minimize risks of adverse events. Stereotaxic microelectrode implantation is an effective surgical approach for the treatment of movement disorders. Stereotaxic head frames are used to increase accuracy of electrode placement and trajectory, and coupled with peri-operative imaging, can be very accurate. Advances in accessibility of 3D printing, robotics, and real time neuroimaging are further improving precision in surgical implantation (66–68).

Parameter optimization is equally important to resolve in the field of therapeutic DBS, and likely accounts for as much variability as anatomical factors. Several animal models of SCI have demonstrated maximal therapeutic responsiveness to low-threshold stimulation for

voluntary locomotion (25, 63, 69). Other studies report that step-wise increases in DBS stimulation frequency of the MLR not only initiate locomotion but increase locomotor frequency (54). There are distinctions between DBS targets CnF and PPN even if their mechanisms are similar. By comparison we found that CnF may be more important than PPN in the initiation and regulation of gait, and facilitating speed of locomotion based on animals' research (43, 70).

Model and stimulation parameters

Other pressing objectives in the field of DBS remains protocol standardization for improved summary of research findings and downstream applications. For example, one review synthesized DBS for Alzheimer's disease, analyzing targets, stimulation frequency, duration, intensity, and treatment time from disease onset (71). While homogeneity of disease may limit such study or protocol synchronicity in humans, animal models for research are an opportunity for consolidation of knowledge generated from a standardized approach, and may thus allow for testing and validation of optimal DBS parameters for human extrapolation. In conjunction with advanced techniques such as MRI and optogenetics for trajectory mapping, refining stimulation parameters may maximize the therapeutic effect of DBS in SCI patients.

Other DBS protocol considerations include the orientation of the electrode relative to the target (28), signal intensity (pulse, frequency and amplitude), and stimulation mode (monopolar, bipolar, tripolar, etc.). For example, in animal models of severe SCI, gait improvements were only achieved with equivalent stimulation current as required to initiate involuntary movement in healthy controls (72). In humans, where device longevity is a concern, bipolar stimulation appears to improve the life of the mean pulse generator compared to monopolar mode (73). DBS parameters not only play an important role in its therapeutic efficacy, they may be as crucial for safety and to prevent off-target adverse events as patient characteristics (surgical and pre-surgical) (74).

Finally, combining DBS with other interventions may enhance the efficacy of DBS as a monotherapy, as has been the case with other electrical neuromodulation approaches. For example, transcutaneous electrical nerve stimulation in combination with functional task practice promotes corticomotor excitability in patients with chronic cervical SCI, though stability of the response was not examined beyond 30 min (75).

In addition to isolated neuromodulatory approaches, combined strategies are theorized to yield significant improvements due to the overlap of spinal locomotor neurons activated during treatment (e.g., DBS/spinal cord stimulation) (44). Indeed, a variety of combinatorial techniques have demonstrated neuroplasticity-driven functional recovery after SCI particularly in corticospinal circuits (31, 54, 76), including combined electrostimulation and pharmacologic approaches (72, 77).

Meanwhile, the demand for pairing radiological imaging with DBS patients continues to grow in order to accommodate the need for personalized evaluation, however the risks aversion of such approaches remain high due to stringent contraindications (78). Recent studies have challenged these manufacturer-based guidelines, providing safety data on 102 patients with no adverse events or DBS impedance, and only a 1.4% intracranial artifact around the implant (79). The initial clinical report on the effects of DBS in patients found that stimulation frequencies >130 Hz were optimal for inducing

locomotor movements (80). However, in various animal models suggesting 40–60 Hz with broad pulse sizes (200–1,000 μ s) was the most efficient range to elicit locomotion (54). Continuing efforts to expand the safe use of radiological imaging include standardization across centers, device specifications, radiofrequency exposure characteristics, magnetic field strengths, and patient positioning protocols. As referred to previously, increased monitoring during DBS is likely to refine and optimize therapeutic efficacy (see Table 1).

Summary

Given that the quality of evidence for DBS for spinal cord injury in humans is very low, and that effective brain targets in animal models are uncertain, recommendations for the use of DBS in SCI patients remain uncertain. To determine the precise effects of DBS-mediated neuroplasticity on functional recovery following spinal cord injury, large-scale clinical trials and studies utilizing large animal models are required. Currently, there are very few clinical reports on DBS-related motor recovery in SCI patients available in databases, the first human clinical trial is underway to assess the impact of DBS on SCI populations (NCT03053791). Based on the literature a proposal for the ideal DBS treatment in SCI candidates may be an individual with motor incomplete SCI (confirmed by clinical and MRI examinations) and preservation of sacral function. In addition, medical imaging of DBS is a major problem, and radiological guidance may be needed to place, evaluate, and reconfigure DBS, particularly in light of more recent developments and intricate directional electrodes. The proposed DBS protocol is predicated on pre-clinical studies which target the MLR/DBS with low frequency (≤ 50 Hz) at medium to broad pulse widths. Optimal stimulation parameters will have to be determined for each patient individually as reference values from human patients are not yet available. Moreover, a strategy to dissect and comprehend the distinct neuronal subpopulations and their exact location for DBS treatment in SCI patients is required, which will clarify the DBS's neuronal targets, in which the MLR has gained scientific and clinical interest as target for DBS to improve motor recovery after SCI with the CNF being proposed as the primary therapeutic target in recent rodent studies. A particular challenge for preclinical translation to human clinical research remains DBS targets accuracy. While the PPN/CNF and their microstructure of rodents are currently well-characterized, the human PPN/CNF is inadequately described (41). Therefore, a more comprehensive description of the macroanatomy and microanatomy of the human MLR is urgently required. Finally, there is a significant trend in combination therapy models, such as the application of DBS during post-injury exercise training, safe pharmacological cocktails or stem cell implantation. The literature reviewed suggest that MLR-DBS combined with rehabilitation methods or EES, including gait rehabilitation or intensive locomotor training, might facilitate motor recovery after SCI. In conclusion, sustained characterization of neuroplasticity after SCI and the development of modulated approaches such as DBS are expected to promote neurological/functional recovery in SCI patients. Certainly, advances in the field of DBS and other methods of electrical neuromodulation have revolutionized the long-held belief that SCI is irreversible.

TABLE 1 The preclinical and clinical study of DBS in SCI.

Study	Study details	Brain target	Physiological changes	Functional changes	Stimulation parameters	Analysis methods for mechanisms
Carmel et al. (81)	Preclinical study: - female rat (225–275 g; n = 10)	Unilaterally-M1 [B:2 mm /3.5 mm]	DBS induced CST axon terminations outgrowth in the ipsilateral spinal cord	DBS improve skilled motor performance following a unilateral SCI	- 333 Hz,0.2 ms duration, - 6 h daily for 10 d	Behavioral testing; neural tracer technology; stereological analysis; regional axon length analysis
Hentall et al. (29)	Preclinical study: - female rat (250–275 g; n = 64) - T8 SCI	Midline-NRM [caudal: 2.3 mm, ventral: 0 mm] R-PAG [ML: 0.7 mm, rostral: 1.2 mm, above the interaural line:4 mm]	DBS (NRM or PAG) promoted the recovery of myelinated axons in perilesional white matter	DBS improve sensory, motor and anatomical recovery following incomplete SCI	- 8 Hz,1 ms,30 μ A - 12 h daily over 4–7 days	Behavioral testing; histological analysis
Bachmann et al. (25)	Preclinical study: - female rat (220–250 g) - T10 SCI	Unilaterally-MLR [B: –7.80 mm, L: +2.00 mm, D: –5.80 mm/0°]	DBS (MLR) activated the supraspinal motor control pathway from the medial brainstem to the lumbar spinal cord	DBS improved the residual locomotor performance after severe SCI	- 25,50,75 and 100 Hz,0.5 ms Awake animals: - 50 Hz, 0.5 ms	Behavioral testing; neural tracer technology; EMG recordings
Noga et al. (44)	Preclinical study: - female rat (240–350 g; n = 28) - T9 SCI	L-MLR [AP:0.7–1.2 mm, ML:2.0 mm, DV:6.2 mm]	DBS (MLR) promoted the presence of theta rhythms in LFPs	DBS improved the locomotion after SCI.	- 10–70 Hz (10, 20, 50 and 70 Hz),0.2, 0.5, 1.0 and 2.0 ms	Behavioral testing; EMG recordings; immunohistochemistry
Wang et al. (30)	Preclinical study: - male rat (250–300 g; n = 36) - T10 SCI.	B-MLR [AP: –7.8 mm, ML: +2.0 mm, DV: –5.0 mm]	DBS improves synaptic plasticity by targeting BDNF, and mTOR	DBS improved hindlimb motor function in SCI rats	- 100 Hz, 0.5 ms - half an hour per day for 4 weeks.	Behavioral testing; western blot
Bonizzato et al. (72)	Preclinical study: - female rat (200–220 g) - T8 SCI.	L-PPN [AP: –7.9 mm $\pm$ 0.05, DV: –6.5 mm, ML: 2 mm]	DBS promotes the reconstruction of the remaining motor circuit	DBS promoted the SCI rats volitional walking	- 40 Hz, 200 μ s, 50–250 μ A - 5 days/week - 30 min /day	Immunohistochemistry; neuromorphological evaluation; electrophysiology
Hofer et al. (31)	Preclinical study: - female rat (220–250 g; n = 127) - T10 SCI	L-CNF [AP: –7.8 mm, DV: –5.1 to –5.5 mm, ML: +2.0 mm]	DBS activated spared descending brainstem fibres	DBS improves motor recovery in the subchronic and chronic SCI phases.	- 50 Hz, 0.5 ms	Behavioral testing; histological analysis; neural tracer technology
Spooner et al. (82)	Clinical study: male patients (40 year; n = 1) - C4 level spinal cord injury	R-PVG [AP: –8.2 mm, lateral: +4.2 mm, vertical: +1.1 mm] B-Cingula [20 mm]	The analgesic effect of DBS on bilateral cingulate gyrus is superior to that of PVG stimulation	DBS improves functional recovery in a complete spinal cord injury	- PVG: 20 Hz - Cingula: 130 Hz - 1-week blinded stimulation trial prior	VAS evaluation

PVG, periventricular gray matter; CNF, cuneiform nucleus; PVG, periventricular gray matter; MLR, mesencephalic locomotor region; PPN, pedunculopontine nucleus; VAS, visual analog scale; B, bilateral; R, right; AP, antero-posterior; L, left; NS, no stimulation; ML, mediolateral; DV, dorsoventral; B, bregma; L, lambda; D, dura; BDNF, brain-derived neurotrophic factor, mTOR, the mammalian target of rapamycin; LFPs, local field potentials.

Author contributions

W-yL: Writing – original draft. W-rQ: Investigation, Writing – review & editing. YL: Investigation, Writing – original draft. S-yW: Investigation, Writing – original draft. D-mL: Data curation, Writing – original draft. L-xD: Writing – review & editing. YW: Writing – original draft, Writing – review & editing.

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Fear of movement in patients after lumbar spine fusion and an analysis of factors: a cross-sectional study

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Background: Numerous studies have confirmed the significant benefits of exercise rehabilitation in both preoperative and postoperative treatment of lumbar disc herniation. However, there is a prevalent fear or avoidance of exercise among patients with chronic low back pain prior to surgery, while research on exercise fear after lumbar fusion remains insufficient. This study aims to investigate the incidence and severity of exercise fear in patients with chronic low back pain and leg pain following lumbar fusion surgery, as well as analyze its underlying mechanism and associated risk factors.

Methods: A cross-sectional study was conducted on patients undergoing posterior lumbar fusion for lumbar disc herniation between May 2023 and January 2024. The Tampa Motor Phobia Scale (TSK-17) was utilized to assess motor fear among participants. Additionally, clinical and imaging risk factors were analyzed through multivariate regression analysis to determine relevant influencing factors.

Results: Following strict inclusion and exclusion criteria, a total of 178 patients who underwent posterior lumbar fusion were included in this study, comprising 104 males (58.4%). Kinesiophobia was defined as a TSK-17 score ≥ 37 , which identified 65.2% (116/178) of the screened patients exhibiting motor phobia. Multivariate regression analysis revealed that motor phobia was strongly associated with age, higher levels of pain intensity, elevated Beck Depression Inventory (BDI) scores, lower General Self-Efficacy Scale (GSES) scores, increased number of surgical levels involved during operation, greater amount of postoperative incision drainage, higher degree of nerve root compression observed on preoperative lumbar MRI scans, as well as smaller area occupied by the paravertebral muscles in the lumbar region.

Conclusion: This study has identified a significantly high incidence of postoperative exercise fear in patients undergoing posterior lumbar fusion, along with potential risk factors. Therefore, it is crucial for clinicians to closely evaluate and monitor these patients in order to develop appropriate strategies for postoperative exercise rehabilitation.

KEYWORDS

kinesiophobia, lumbar interbody fusion, low back pain, rehabilitation, cross-sectional study

Introduction

Lumbar interbody fusion (LIF) is a primary surgical technique for treating Lumbar disc herniation (LDH), which has demonstrated significant efficacy and widespread clinical application (1). LIF surgery effectively alleviates clinical symptoms, prevents neurological function deterioration by fully decompressing the dural sac and nerve roots compressed by the intervertebral disc's nucleus pulposus, and achieves stable internal fixation and reliable fusion (2, 3). With an increasing incidence of LDH in younger individuals and an aging population, there has been a steady rise in the number of LIF surgeries performed annually, leading to a growing demand for postoperative rehabilitation (4, 5). Numerous studies have confirmed that exercise rehabilitation plays a crucial role in both pre- and post-operative treatment of lumbar disc herniation (6). Postoperative exercise rehabilitation is an essential component of non-pharmacological therapy aimed at enhancing lower back muscle strength, improving lumbar spine stability, reducing postoperative pain, enhancing lumbar function recovery, and ultimately improving patients' quality of life (7–9). Typically initiated upon patient awakening from anesthesia after lumbar surgery with focus on the first six months following surgery. Early exercises primarily involve axis turning as well as sitting-to-standing transitions training. Subsequently progressing to standing up from bed followed by walking exercises. Other therapeutic exercises include early ankle pump exercises along with single straight leg raises while double straight leg raises are introduced during intermediate stages. Later stages incorporate yoga ball training into the program (10).

Kinesiophobia refers to an excessive, irrational fear and avoidance of movement or activity that can be debilitating (11). During the acute stage of pain, fear of exercise serves as a defensive behavior strategy to protect the body from further injury (12). However, in the long term, it becomes detrimental as it may lead to decreased motor function and disability due to lack of physical activity, while also increasing the risk of depression and anxiety (13). Research has demonstrated a positive correlation between the severity of kinesiophobia and postoperative pain intensity and dysfunction, while negatively impacting quality of life (13, 14).

Kinesiophobia is prevalent in the preoperative phase of patients with chronic Low Back Pain (LBP) (15). Even after surgical intervention to relieve pathological compression, a significant number of patients continue to exhibit preoperative exercise psychology and behavior (16, 17). A study (12) revealed that LBP patients with high levels of exercise phobia had a 41% higher risk of physical disability compared to those without exercise phobia. Given that Lumbar Interbody Fusion (LIF) entails longer duration and greater trauma than simple discectomy or decompression, it results in worse lower back muscle strength and increased damage, making early motor rehabilitation particularly crucial (18). Currently, there is insufficient research on exercise fear among patients following LIF surgery, with most studies limited to investigating patient compliance with exercise rehabilitation training. Previous studies have identified kinesiophobia as an important factor influencing compliance with exercise rehabilitation in chronic LBP patients; however, few studies have explored the occurrence of kinesiophobia specifically in post-LIF surgery patients. Furthermore, existing studies primarily analyze the relationship between exercise fear and

subjective variables such as pain, self-care ability, social support, and emotion while neglecting objective imaging variables. The decline in function observed in key core muscles like multifidus and erector spinae is closely associated with LBP (19). Fear of exercising can exacerbate low back pain symptoms after surgery; nevertheless, whether there exists a causal relationship between lumbar and dorsal muscles' condition and post-surgery fear of exercising remains unexplored.

Therefore, the objective of this study is to comprehensively investigate the prevalence of kinesiophobia in patients following lumbar interbody fusion (LIF) by considering demographic characteristics, general clinical data, and imaging parameters. Additionally, we aim to analyze the factors influencing kinesiophobia and provide guidance for healthcare professionals to promptly implement intervention measures such as health education and exercise rehabilitation programs for high-risk individuals. Ultimately, our goal is to prevent delayed recovery or dysfunction of the lumbar spine caused by exercise phobia.

Methods

Study population

A cross-sectional study was conducted on patients with lumbar disc herniation who underwent posterior lumbar fusion surgery at our orthopedic center between May 2023 and January 2024. This study received ethical approval from our hospital's Ethics Committee (Approval number: 2022-119), and all participants were provided with informed consent before voluntarily participating in the study.

The inclusion criteria for this study were as follows: (1) Lumbar disc herniation was diagnosed based on clinical symptoms, with a disease duration of more than 3 months, regardless of the presence or absence of lumbar spinal stenosis; (2) Pathological anatomical features corresponding to clinical symptoms were confirmed by clear and accurate MRI imaging; (3) Surgical indications for posterior lumbar interbody fusion were met: A history of lumbar intervertebral disc protrusion for more than 6 to 12 weeks, with no effect after systematic conservative treatment; or symptoms worsen or recur during conservative treatment; or severe pain, or the patient is in a forced position, affecting work or life; or single nerve paralysis or cauda equina nerve paralysis occurs, manifested as muscle paralysis or rectal and bladder symptoms; (4) Participants aged between 18 and 70 years old were included.

Exclusion criteria: (1) Cognitive impairment, disturbance of consciousness, or mental disorder will be grounds for exclusion; (2) Refusal to participate in the study will result in exclusion; (3) Communication disorders will lead to exclusion; (4) Inability to complete the planned operation due to any reason will be considered as an exclusion criterion; (5) Coexistence of other acute traumas such as spinal fracture and hip fracture will result in exclusion; (6) Lower limb muscle strength less than grade 3 before operation and less than grade 4 after operation will serve as an exclusion criterion; (7) Previous history of spinal surgery is a ground for exclusion; (8) Presence of severe osteoarthritis, infection, tuberculosis, malignant tumor, heart failure, pulmonary dysfunction, muscle atrophy or any medical condition that may interfere with exercise are all reasons for potential exclusions.

Data collection and outcome measures

We extracted comprehensive clinical data from the patient's electronic medical record system, encompassing gender, age, height, weight, marital status, education level, disease duration, occupation (manual or mental worker), primary caregiver information, operative segment details, number of postoperative wound drainage tubes employed, total postoperative wound drainage volume recorded, current analgesic usage patterns and comorbidities (Charlson comorbidity index score was calculated). Additionally collected were factors potentially influencing motor and neurologic recovery such as alcohol and smoking history pre- and post-hospitalization.

The clinical outcome data encompassed pain experienced during exercise, the onset of exercise-induced pain, and the Oswestry Disability Index (ODI) (20). Pain intensity was assessed using a visual analogue scale (VAS, 1–10). Subjective emotional factors that could potentially impact postoperative exercise were evaluated through the use of the General Self Efficacy Scale (GSES) (21) and Beck Depression Inventory (BDI-13) (22).

Assessment of kinesiophobia

The Tampa Scale of Kinesiophobia (TSK-17) (23) was utilized to evaluate the presence of kinesiophobia, a self-reported questionnaire comprising 17 items categorized into four response options: strongly agree, agree, disagree, and strongly disagree. Each item was scored on a scale ranging from 1 to 4. Items 4, 8, 12, and 16 were reverse-scored. Total scores ranged from 17 to 68 with higher scores indicating greater severity of kinesiophobia. The TSK-17 is widely recognized as a reliable measure for assessing kinesiophobia (24, 25). A total TSK-17 score equal to or exceeding 37 indicates the presence of kinesiophobia. The Chinese version of TSK-17 (26) demonstrated strong internal consistency (Cronbach's α coefficient = 0.82) and test-retest reliability (intraclass correlation coefficient ICC = 0.90). In this study, patients were classified into two groups based on their TSK-17 scores: the kinesiophobia group (TSK-17 score $\geq$ 37) and the non-kinesiophobia group (TSK-17 score $\leq$ 36).

Radiology assessment

The patient's preoperative lumbar spine MRI was acquired from the hospital imaging system HIS for the assessment of nerve root compression and lumbar paravertebral core muscle area in the patient.

Grading of nerve root compression was assessed based on the research criteria established by Pfirrmann et al. (27). The degree of nerve root compression was evaluated using MRI cross-sectional imaging of the segment with the most severe lumbar disc herniation, which was categorized into four grades ranging from 0 to III: grade 0 (normal) indicated no evident contact between the disc and the nerve root; Grade I (contact) denoted that although the disc was adjacent to the nerve root, there were no signs of deviation or deformation in the nerve root; Grade II (offset) indicated displacement of the nerve root due to disc compression; Grade III (compression) referred to flattening of the nerve root caused by compression from both nucleus pulposus and vertebral canal wall. Compared with measuring the sagittal

diameter index (SI) (28, 29), this method is more intuitive and convenient to evaluate the degree of nerve root compression.

Lumbar core muscle area (bilateral multifidus and erector spinae) data were collected. Prior to the operation, all patients underwent a lumbar MRI plain scan using a Siemens 3.0 T MRI imager with T2 sequence parameters: repeat time of 3,500 ms, echo time of 94 ms, and a scan matrix of 256×51 . The MRI scanning axis was kept parallel to the endplate of the lumbar spine, and fifteen images were scanned in axial position (3 images of the upper, central and lower part of each intervertebral space). In this study, the morphology and structure of the multifidus and erector spinae muscles at the central level of the L4/5 intervertebral space were measured on bilateral cross sections (Figure 1). Compared with the images of the upper and lower layers of the intervertebral space, the images of the central level of the intervertebral space avoided the vertebral body, and the muscle area imaging was fuller and clearer. To minimize potential bias caused by different body positions, patients were positioned in a prone position during the MRI examination. All imaging measurements were performed by an investigator who was not involved in patient treatment.

Statistical analysis

The statistical analysis was performed using SPSS 25.0 software. Continuous variables with a normal distribution were described as mean $\pm$ standard deviation ($X \pm S$) and compared using an independent t-test. Non-normally distributed continuous variables were described as median (quartile) [M (P25, P75)], and group comparisons were analyzed using the Mann-Whitney U test. Categorical variables were presented as frequency (%) and analyzed using either Pearson chi-square test or Fisher's exact test. Binary logistic regression was employed to analyze the factors influencing postoperative kinesiophobia in patients. A significance level of $\alpha = 0.05$ was used, with $p < 0.05$ considered statistically significant.

Results

Between May 2023 and January 2024, patients who met the predefined inclusion and exclusion criteria were consecutively enrolled in the study, with prospective collection of their postoperative information. During this period, a total of 1,022 patients were admitted to our hospital for spinal diseases. Among them, we initially enrolled 193 patients with lumbar interbody fusion (LIF), but excluded 12 patients who had undergone MRI at other hospitals and 3 patients who experienced postoperative cerebrospinal fluid leakage and subsequently withdrew from the study. Ultimately, a total of 178 eligible patients were included in the analysis. The demographic characteristics, clinical profiles, and imaging parameters of these enrolled participants are presented in Table 1.

Incidence and influencing factors of kinesiophobia after LIF

Among the 178 elderly patients, a total of 116 individuals were screened for TSK-17 scores $\geq$ 37 points, revealing that motor phobia was present in 65.2% of these patients following LIF

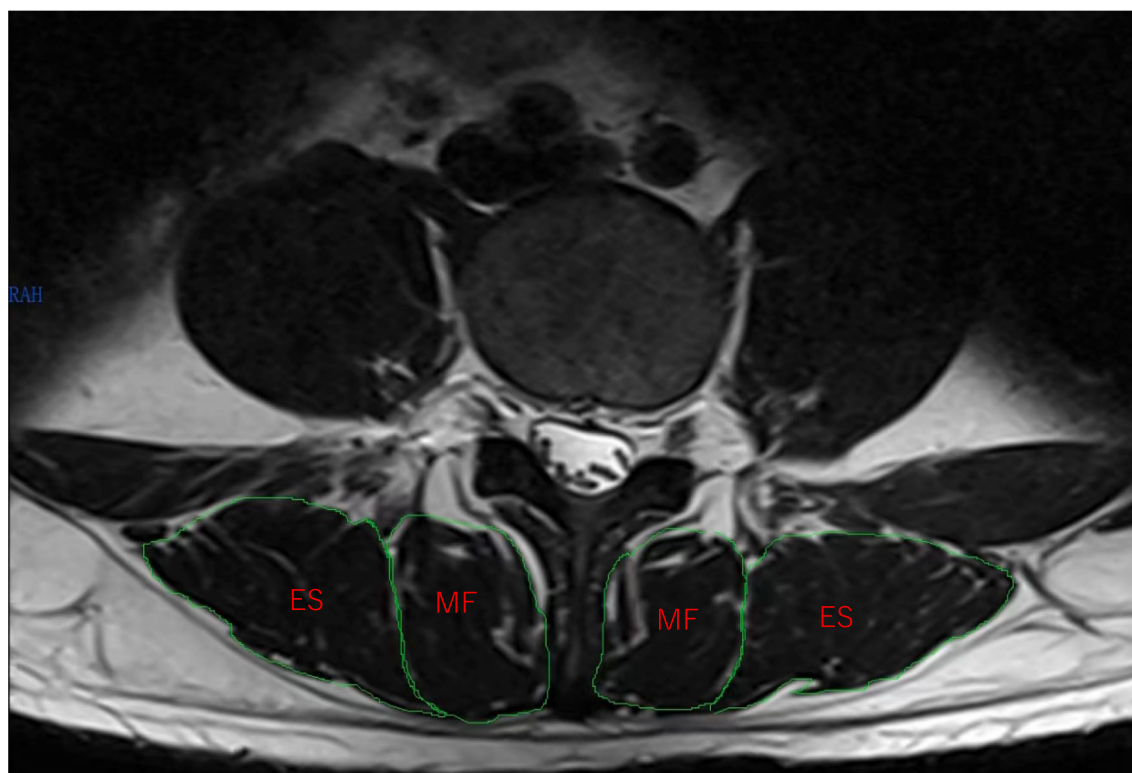


FIGURE 1

Cross-sectional magnetic resonance imaging of the fourth lumbar spine. MF, multifidus; ES, erector spinae.

(Table 1). The results from univariate analysis demonstrated significant differences between the kinesiophobia group and the non-kinesiophobia group in terms of age, number of surgical levels, postoperative drainage volume, VAS score, GSES score, BDI score, ODI score, degree of nerve root compression and total ES + MF area ($p < 0.05$) (Table 2).

In order to further investigate the correlation between the 9 variables exhibiting single factor differences and the occurrence of kinesiophobia, as well as to explore their relationship, we employed a binary logistic regression model (Table 3). The occurrence of kinesiophobia was considered as the dependent variable, while the 9 variables with single factor differences were treated as independent variables. All data were standardized prior to conducting binary logistic regression analysis.

The binary logistic regression analysis revealed that advanced age (OR = 3.883 (1.678–8.985), $p = 0.002$), higher VAS score (OR = 4.401 (1.706–11.357), $p = 0.002$), elevated BDI score (OR = 3.969 (1.225–12.859), $p = 0.022$), reduced GSES score (OR = 0.330 (0.135–0.807), $p = 0.015$), increased number of operative levels (OR = 2.106 (1.058–4.194), $p = 0.034$) and increased postoperative incision drainage (OR = 3.724 (1.374–10.294), $p = 0.011$), greater degree of nerve root compression on preoperative lumbar MRI (OR = 4.916 (2.257–10.710), $p < 0.001$), and smaller lumbar paravertebral muscle area (OR = 0.508 (0.262–0.984), $p = 0.045$) were independent risk factors for postoperative motor phobia. However, Oswestry Disability Index (OID) score was not an independent factor affecting postoperative kinesiophobia ($p > 0.05$).

Discussion

Lumbar disc herniation is a degenerative disease of the lumbar spine, characterized by low back pain (LBP) as the primary symptom, and it is a prevalent clinical condition in orthopedics. This condition primarily affects individuals between 25 to 55 years old, with a higher incidence among males than females. Approximately 10 to 20% of patients require surgical intervention (30), and postoperative exercise rehabilitation plays a crucial role in facilitating early return to work. However, fear and avoidance behaviors toward exercise after surgery hinder compliance with rehabilitation exercises, impede the recovery of lower back muscles (31), and fail to alleviate residual pain symptoms postoperatively, leading to prolonged impairment of motor function and perpetuating a vicious cycle (31). In this study, motor phobia was observed in 65.2% of patients following lumbar interbody fusion (LIF), which aligns closely with findings reported by Kemani et al. (31) but slightly exceeds those reported by Svensson et al. (32) and Lv et al. (33) for simple lumbar discectomy and elderly patients with primary osteoporosis, respectively. Notably, the prevalence of kinesiophobia among patients with chronic heart failure or chronic obstructive pulmonary disease surpasses that reported by Fatih et al. (34). The rationale behind this discrepancy may be attributed to LIF being more invasive compared to simple lumbar discectomy; furthermore, patients undergoing LIF may possess an increased desire for self-protection when compared to non-surgical counterparts due to perceiving safety as paramount during physical activities given the high-risk nature associated with LIF surgery (35).

TABLE 1 Fundamental demographic, clinical characteristics, and imaging parameters of the enrolled patients.

Variable	Value	n (%)/($\bar{x} \pm S$)/M (P25, P75)
Gender	Male	104 (58.4)
	Female	74 (41.6)
Age (YO)		59.629 $\pm$ 10.723
BMI (kg/m ²)		24.234 $\pm$ 3.022
Marriage status	Married	168 (94.4)
	Unmarried	4 (2.2)
	Divorced	6 (3.4)
Care provider	Spouse	84 (47.2)
	Children	84 (47.2)
	Others	10 (5.6)
Education level	Junior high school and below	106 (59.6)
	High school	39 (21.9)
	College	27 (15.2)
	Bachelor	6 (3.4)
Job category	None	68 (38.2)
	Primary mental work	30 (16.9)
	Primary physic work	80 (44.9)
Preoperative smoking history	No	133 (74.7)
	Yes	45 (25.3)
Postoperative smoking history	No	156 (87.6)
	Yes	22 (12.4)
Preoperative drinking history	No	160 (89.9)
	Yes	18 (10.1)
Postoperative drinking history	No	172 (96.6)
	Yes	6 (3.4)
LDH with lumbar spinal stenosis	No	30 (16.9)
	Yes	148 (83.1)
Side	Left	63 (35.4)
	Right	68 (38.2)
	Bilateral	47 (26.4)
Disease duration		10.00 (3.00,36.00)
Operative level		2.494 $\pm$ 0.928
Postoperation	Within 1wk	14 (7.9)
	1 ~ 4 wks	82 (46.1)
	1 ~ 3 mons	76 (42.7)
	3 ~ 6 mons	6 (3.4)
Number of drainage tubes		1.882 $\pm$ 0.490
Total amount of wound drainage (mL)		504.933 $\pm$ 223.790
Usage of painkiller pills	None	55 (30.9)
	NSAIDs	110 (61.8)
	Pregabalin	1 (0.6)
	NSAIDs + Pregabalin	9 (5.1)
	Opiates	3 (1.7)

(Continued)

TABLE 1 (Continued)

Variable	Value	<i>n</i> (%)/($\bar{x} \pm S$)/M (P25, P75)
Diabetes	No	145 (81.5)
	Yes	33 (18.5)
CHD	No	165 (92.7)
	Yes	13 (7.3)
Hypertension	No	117 (65.7)
	Yes	61 (34.3)
COPD	No	169 (94.9)
	Yes	9 (5.1)
Arthritis	No	174 (97.8)
	Yes	4 (2.2)
Hepatitis	No	173 (97.2)
	Yes	5 (2.8)
CCI score		2.00 (1.00,3.00)
Exercise with pain	Yes	62 (34.8)
	No	116 (65.2)
Onset time of pain after exercise (min)		30.00 (10.00,30.00)
ODI score		16.00 (12.00,24.00)
VAS score		2.00 (1.00,3.00)
GSES score		24.236 $\pm$ 6.024
BDI score		3.00 (1.00,8.00)
Grading of lumbar nerve root compromise		1.972 $\pm$ 1.132
ES + MF area (mm ²)		3696.380 (3153.340,4131.400)

The incidence of kinesiophobia varies across different countries, regions, surgical procedures, and disease types. This study reveals a high prevalence of kinesiophobia among patients after lumbar interbody fusion (LIF) in our region. Given the increasing age of individuals with lumbar disc herniation and the aging population, it is crucial to recognize the significant detrimental effects of kinesiophobia. The objective of this study was to investigate the incidence of kinesiophobia in LIF patients and identify associated risk factors to gain further insights into its underlying mechanisms. Our findings indicate that advanced age, higher visual analog scale (VAS) scores for pain intensity, elevated Beck Depression Inventory (BDI) scores, increased General Self-Efficacy Scale (GSES) scores, multiple operative segments involved, greater postoperative incision drainage volume, reduced paravertebral muscle area size, and heightened preoperative nerve root compression levels are all independent risk factors for postoperative motor phobia in LIF patients.

The present study revealed a positive correlation between age and the incidence of motor phobia following LIF, which aligns with Alpalha et al.'s findings (36) that physically frail patients and the elderly, particularly those residing in nursing homes, exhibit higher levels of kinesiophobia. Furthermore, previous studies (34) have demonstrated that age significantly influences kinesiophobia levels in patients with chronic heart failure (44.3%) and chronic obstructive pulmonary disease (47.7%). Jenevi et al. (16) observed that individuals aged 56–65 years displayed higher levels of kinesiophobia compared to other age groups, while those over 65 years exhibited even greater levels. Additionally, advanced age may be associated with reduced

cognitive function and health information processing abilities (37). Bilgin et al.'s research (26), involving a questionnaire survey on 504 non-surgical patients suffering from neck and low back pain, indicated that individuals with lower educational attainment tend to experience heightened kinesiophobia. However, our study did not identify education level as an independent risk factor for kinesiophobia among LIF patients; furthermore, no significant differences were found in the incidence of post-LIF kinesiophobia across different education levels. These results are consistent with John et al.'s findings (16), suggesting variations in health education experiences related to lumbar spine conditions among subjects with differing educational backgrounds. Notably, individuals with lower educational attainment may benefit from systematic exercise programs and pain self-management health education training conducted by medical professionals (including redefining pain physical examination procedures, scientifically assessing pain severity levels, implementing appropriate pain response measures tailored to individual needs) leading to a reduction in their overall level of kinesiophobia (38).

In this study, there was a positive correlation between the severity of depression (as measured by BDI) and the prevalence of exercise fear following lumbar interbody fusion (LIF), which aligns with findings reported by Bilgin et al. (39). Patients with severe lumbar disc herniation often experience prolonged low back pain, leading to reduced engagement in daily activities and social interactions. Consequently, they develop apprehension toward postoperative exercise rehabilitation due to concerns about potential harm to their bodies. Moreover, depression can intensify pain perception, thereby contributing to the development of exercise

TABLE 2 Association between Tampa Scale of Kinesiophobia index score and related factors.

Variable	Value	TSK < 37 (n = 62)	TSK ≥ 37 (n = 116)	$\chi^2/t/Z$	p value
Gender				3.399*	0.065
	Male	42 (67.7)	62 (53.4)		
	Female	20 (32.3)	54 (46.6)		
Age (YO)		51.452 ± 11.219	64.000 ± 7.409	−7.931 [†]	0.000
BMI (kg/m ²)		24.404 ± 3.338	24.144 ± 2.850	0.547 [#]	0.585
Marriage status				3.722*	0.155
	Married	58 (93.5)	110 (94.8)		
	Unmarried	3 (4.8)	1 (0.9)		
	Divorced	1 (1.6)	5 (4.3)		
Care provider				3.217*	0.200
	Spouse	26 (41.9)	58 (50.0)		
	Children	30 (48.4)	54 (46.6)		
	Others	6 (9.7)	4 (3.4)		
Education level				4.492*	0.213
	Junior high school and below	39 (62.9)	67 (57.8)		
	High school	15 (24.2)	24 (20.7)		
	College	5 (8.1)	22 (19.0)		
	Bachelor	3 (4.8)	3 (2.6)		
Job category				4.287*	0.117
	None	21 (33.9)	47 (40.5)		
	Primary mental work	7 (11.3)	23 (19.8)		
	Primary physic work	34 (54.8)	46 (39.7)		
Preoperative smoking history				0.060*	0.807
	No	47 (75.8)	86 (74.1)		
	Yes	15 (24.2)	30 (25.9)		
Postoperative smoking history				0.100*	0.751
	No	55 (88.7)	101 (87.1)		
	Yes	7 (11.3)	15 (12.9)		
Preoperative drinking history				2.911*	0.088
	No	59 (95.2)	101 (87.1)		
	Yes	3 (4.8)	15 (12.9)		
Postoperative drinking history				1.921*	0.166
	No	62 (100.0)	110 (94.8)		
	Yes	0 (0.0)	6 (5.2)		
LDH with lumbar spinal stenosis				0.425*	0.515
	No	12 (19.4)	18 (15.5)		
	Yes	50 (80.6)	98 (84.5)		
Side				0.121*	0.941
	Left	23 (37.1)	40 (34.5)		
	Right	23 (37.1)	45 (38.8)		
	Bilateral	16 (25.8)	31 (26.7)		
Disease duration		7.00 (3.00,24.00)	10.00 (3.00,46.00)	−0.496 ^Δ	0.620
Operative level		2.097 ± 0.740	2.707 ± 0.951	−4.730 [†]	0.000

(Continued)

TABLE 2 (Continued)

Variable	Value	TSK < 37 (<i>n</i> = 62)	TSK ≥ 37 (<i>n</i> = 116)	$\chi^2/t/Z$	<i>p</i> value
Postoperation				6.010*	0.111
	Within 1wk	2 (3.2)	12 (10.3)		
	1 ~ 4 wks	25 (40.3)	57 (49.1)		
	1 ~ 3 mons	32 (51.6)	44 (37.9)		
	3 ~ 6 mons	3 (4.8)	3 (2.6)		
Number of drainage tubes		1.952 ± 0.493	1.845 ± 0.486	1.388*	0.167
Total amount of wound drainage (mL)		367.790 ± 177.446	578.233 ± 211.710	−6.672*	0.000
Usage of painkiller pills				2.437*	0.752
	None	19 (30.6)	36 (31.0)		
	NSAIDs	41 (66.1)	69 (59.5)		
	Pregabalin	0 (0.0)	1 (0.9)		
	NSAIDs + Pregabalin	2 (3.2)	7 (6.0)		
	Opiates	0 (0.0)	3 (2.6)		
Diabetes				3.310*	0.069
	No	55 (88.7)	90 (77.6)		
	Yes	7 (11.3)	26 (22.4)		
CHD				0.345*	0.557
	No	56 (90.3)	109 (94.0)		
	Yes	6 (9.7)	7 (6.0)		
Hypertension				1.159*	0.282
	No	44 (71.0)	73 (62.9)		
	Yes	18 (29.0)	43 (37.1)		
COPD				0.208*	0.649
	No	60 (96.8)	109 (94.0)		
	Yes	2 (3.2)	7 (6.0)		
Arthritis				0.000*	1.000
	No	61 (98.4)	113 (97.4)		
	Yes	1 (1.6)	3 (2.6)		
Hepatitis				0.000*	1.000
	No	60 (96.8)	113 (97.4)		
	Yes	2 (3.2)	3 (2.6)		
CCI score		2.00 (1.00,3.00)	2.00 (0.00,3.00)	−0.191 ^Δ	0.848
Exercise with Pain				0.735*	0.391
	Yes	19 (30.6)	43 (37.1)		
	No	43 (69.4)	73 (62.9)		
Onset time of pain after exercise (min)		25.00 (10.00,30.00)	30.00 (10.00,30.00)	−1.535 ^Δ	0.125
ODI score		15.00 (11.00,18.00)	17.00 (13.00,27.50)	−2.412 ^Δ	0.016
VAS score		1.00 (0.00,2.00)	3.00 (2.00,3.00)	−7.389 ^Δ	0.000
GSES score		27.919 ± 5.695	22.267 ± 5.236	6.654*	0.000
BDI score		2.00 (0.00,4.00)	5.00 (2.00,9.00)	−4.140 ^Δ	0.000
Grade of lumbar nerve root compromise		1.19 ± 1.053	1.62 ± 1.027	−2.620*	0.010
ES + MF area (mm ²)		3846.38 (3453.34,4173.18)	3648.34 (3071.92,4076.98)	−2.513 ^Δ	0.012

*Chi-square test, #: t-test, ^Δ: Z test.

TABLE 3 Influencing factors of kinesiophobia in patients after LIF: binary logistic regression analysis.

Variable	B	SE	Wald	OR	95%CI		p
					Lower limit	Upper limit	
Age (YO)	1.357	0.428	10.044	3.883	1.678	8.985	0.002
Operative level	0.745	0.351	4.495	2.106	1.058	4.194	0.034
Total amount of wound drainage (mL)	1.315	0.519	6.423	3.724	1.347	10.294	0.011
VAS score	1.482	0.484	9.389	4.401	1.706	11.357	0.002
GSES score	−1.107	0.456	5.908	0.330	0.135	0.807	0.015
BDI score	1.379	0.600	5.283	3.969	1.225	12.859	0.022
ODI score	−0.446	0.0393	1.286	0.640	0.296	1.384	0.257
Grade of lumbar nerve root compromise	1.593	0.397	16.072	4.916	2.257	10.710	<i>P</i> <0.001
ES + MF area (mm ²)	−0.678	0.338	4.037	0.508	0.262	0.984	0.045
Constant	2.206	0.494	19.947	0.000			9.075

B, Beta; SE, Standard Error; OR, Odds Ratio; CI, Confidence Interval. R² = 0.596, Adjusted R² = 0.824, *p* < 0.001.

phobia associated with pain. Notably, individual self-efficacy emerged as a protective factor against kinesiophobia in our study. Self-efficacy refers to an individual's confidence in their ability to achieve desired outcomes and diminished self-efficacy has been identified as a predictor for long-term disability (40). Previous research has confirmed that self-efficacy acts as a mediating variable between pain-related fear and avoidance behavior among patients with chronic low back pain (41). Individuals with high levels of self-efficacy exhibit greater activity levels, work endurance, efficiency in exercising/stretching routines, and coping strategies. Furthermore, exercise fear and avoidance can impede individuals' participation in meaningful activities while increasing negative affective states and reducing self-efficacy levels; ultimately exacerbating pain symptoms and perpetuating a vicious cycle.

Pain is a significant influential factor in the development of kinesiophobia (11), and this study's findings align with this notion. However, our study revealed that the presence and timing of pain during exercise were not independent factors contributing to kinesiophobia; rather, it was the intensity of pain that emerged as an independent determinant. This implies that individuals experiencing higher levels of pain exhibit greater fear toward engaging in physical activity, with such fear stemming from heightened levels of pain-related apprehension. Previous research has indicated that even after successful surgical interventions, 10 to 40% of patients continue to report persistent pain complaints (37). The persistence of postoperative residual pain can be attributed to various factors including preoperative physiological and anatomical damage severity, surgical variables, as well as psychological and social influences. The fear-avoidance model (42) elucidates the underlying psychological mechanisms whereby individuals with elevated levels of pain-related fear demonstrate biased attentional and cognitive evaluations toward their discomfort, thereby perpetuating both their experience of pain and functional impairments. Notably, individuals exhibiting high levels of pain-related fear exhibit increased activation within the anterior insula and central cingulate cortex when evaluating painful stimuli as potential threats.

Therefore, the intensity of pain stimulus is perceived as heightened, leading to increased vigilance toward pain signals in both internal and external environments. Even after physiological healing has occurred, individuals continue to interpret pain as indicative of tissue damage progression. However, it should be noted that fear associated with pain does not always result in avoidance behavior;

patients experiencing mild to moderate pain may modify their behavior based on self-determined goals. When individuals perceive the value of engaging in target behaviors to outweigh the importance of avoiding pain, they reject avoidance behavior and prioritize participation in exercise training for rehabilitation (43).

In this study, the majority of subjects underwent surgery between 1 and 12 weeks postoperatively, during which time they had their wound drainage tubes removed and were able to ambulate. The patients' wound healing varied over time, despite following rehabilitation exercise instructions tailored to their specific postoperative period with gradually increasing difficulty. However, patients who were closer to the operation date still expressed concerns about poor wound healing and bleeding caused by exercise. Previous studies have indicated a strong correlation between increased placement of drainage tubes after surgery and higher rates of surgical site infection (44). Additionally, greater incision drainage following surgery may indicate more vascular injury, impaired coagulation function, and lower hemoglobin levels in patients (45). Consequently, such patients tend to be more cautious after surgery as they associate exercise with potential harm or injury and may therefore avoid it altogether. It is important to note that inappropriate exercises like weight lifting, twisting movements, rugby or other contact sports pose certain risks for screw displacement as well as recurrent disc herniation or rupture after lumbar surgery (46). Patients undergoing multiple surgical segments with several postoperative incisions require guidance from professional rehabilitation therapists for safe exercise practices. This approach not only helps alleviate fear associated with exercising but also prevents unnecessary sports-related injuries.

However, in certain individuals, the recovery of pathological anatomical features in the lumbar spine does not necessarily exhibit a direct correlation with a reduction in pain complaints. This is exemplified by "Failed back surgery syndrome" (FBSS), which denotes persistent axial or peripheral pain following anatomically successful surgical procedures (47). Although LIF can alleviate compression of the intervertebral disc on the nerve root within the spinal canal, it may not instantaneously eradicate nerve root symptoms. A retrospective analysis conducted by Jonsson et al. (11) revealed that 40% of patients experienced enduring back or leg pain after undergoing lumbar disc surgery (48), thereby partially impeding their active movement behavior.

The paravertebral muscle area at the L4 and L5 levels exhibited a significant association with kinesiophobia, as numerous studies have

demonstrated that low back pain (LBP) is linked to alterations in paravertebral muscles. A smaller paravertebral muscle area corresponds to weaker lumbar and back muscle strength, which is a crucial factor contributing to low back pain, lumbar degeneration, and dysfunction (49, 50). In this study, we specifically focused on the lumbar core muscles and aimed to establish a direct correlation between paravertebral muscles and exercise phobia. Our findings revealed that both total areas of the paravertebral muscles acted as protective factors against postoperative kinesiophobia. This observation further supports the relationship between the lumbar motor core muscle area and kinesiophobia. Additionally, research has indicated that atrophy of the paraspinal muscles can lead to altered biomechanical properties and lumbar instability, potentially representing the pathological mechanism underlying impaired motor function in patients with lumbar disc herniation (LDH). Furthermore, surgical treatment itself may reduce the cross-sectional area of paraspinal muscles resulting in weakness (51) and stiffness (52).

Additionally, low back pain resulting from the compression of nerve roots in the lumbar intervertebral disc's nucleus pulposus is a prevalent manifestation among typical patients with lumbar disc herniation (LDH) (53). This condition significantly restricts their engagement in meaningful daily activities prior to surgery. These pain and movement disorders are typically chronic in nature. Although most radicular pain is immediately relieved after surgery, patients may require more time to adapt due to sudden changes in their movement habits post-surgery. Therefore, for the rehabilitation treatment of LIF patients, it may be necessary to implement multimodal rehabilitation measures such as cognitive-behavioral intervention therapy, exercise rehabilitation, and case management (54, 55) to alleviate postoperative pain and fear while facilitating an early return to work.

This study has several inherent limitations. Firstly, this study only included patients with lumbar disc herniation (LDH) from a single center, which may introduce selection bias and limit generalizability to other populations. Secondly, we did not investigate the exercise environment of the included patients, which could potentially act as a confounding factor. Lastly, due to the short follow-up period in this study, it is not representative of exercise fear experienced by patients 1–2 years or longer after lumbar interbody fusion (LIF) surgery nor does it capture dynamic changes in exercise fear at different time points post-surgery. Despite these limitations, this study holds clinical relevance as it provides real-world observations on post-LIF patients in China. In future research endeavors, multi-center studies with larger sample sizes are warranted along with cohort or case–control studies exploring psychological and physiological factors.

Conclusion

In conclusion, our findings indicate that motor phobia is present in 65.2% of patients with lumbar disc herniation (LDH) following lumbar interbody fusion (LIF). Furthermore, the results of multivariate analysis reveal that advanced age, greater pain severity, higher scores on the Beck Depression Inventory (BDI), lower scores on the General Self-Efficacy Scale (GSES), increased number of surgical levels, higher incidence of postoperative incision drainage, elevated transverse nerve root compression observed on preoperative lumbar magnetic resonance imaging (MRI), and reduced area of the

lumbar paravertebral muscles are independently associated with motor phobia. To enhance postoperative functional recovery in LDH patients undergoing LIF and reduce disability rates while improving their quality of life, early identification of individuals at high risk for kinesiophobia is crucial. Implementing interventions such as cognitive-behavioral therapy, exercise rehabilitation management, and preoperative adaptive exercise training should be considered.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the ethic committee of Hunan Provincial People's Hospital, the First Affiliated Hospital of Hunan Normal University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YP: Conceptualization, Writing – original draft. QQ: Data curation, Writing – original draft. CY: Formal analysis, Writing – original draft. MD: Data curation, Writing – original draft. HZ: Formal analysis, Writing – original draft. JW: Investigation, Writing – review & editing. HQ: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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